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Drug Repurposing for the treatment of Lung Cancer – A Review

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Abstract

The amount spent on cancer medication has doubled in the last five years. With the average cost of a new drug released in the market being $100,000 in 2017, it is no surprise that the costs for cancer treatment are exorbitant. Even the newer cancer medications are not always successful. Hence there is a need to find chemotherapeutic agents which are more economical and attainable to patients. Repurposing drugs from other non-cancer treatments may prove to be the fastest and most affordable choice. Medications from non-cancer treatments may have secondary targets which can be exploited for the treatment of cancer. This review focusses on four different classes of drugs for the treatment of lung cancer: antibiotics, anti-depressants, anti-psychotics and anti-parasitic. Candidates from each of these classes are chosen through computational and bioinformatic methods by analyzing the modes of action and determining their secondary targets. The scope of drug repurposing and their use in lung cancer therapy is discussed in this article.

Keywords: Lung cancer; Antibiotics; Drug repurposing; Blood vessels; Adenocarcinoma; Squamous cell carcinoma

Introduction

Lung cancer is one of the most widely occurring type of cancer, third only to breast and cervical cancers [1]. According to World Health Organization, more than 1.6 million people have died of lung cancer since 2015 [2] and an estimated 2 million new lung cancer cases since then [3]. Lung cancer is responsible for 14% of all cancer incidents and 25% of cancer deaths [4]. Most lung cancers are diagnosed at advanced stages. Multiple parts of the bronchial tree can be affected, causing variable symptoms. Since the lungs are in close contact with the major blood vessels, metastasis (or invasion of cancer cells into neighboring tissues) is a highly probable event. This invasive nature of lung cancer makes it difficult for targeted detection and therapy in patients.

The two major types of lung cancer are - small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [4]. SCLC is a type of neuroendocrine tumor that originates from the bronchi, is highly aggressive and is reported to be seen mostly in patients who smoke. SCLC accounts for 15% of all lung cancer cases [4]. On the other hand, NSCLC originates mostly from the periphery of the lung, develops slowly and usually shows no symptoms until the disease has advanced [5]. NSCLC included other subtypes of cancer such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. It is mostly seen in the non-smoking population and is mainly due to second hand smoke [5].

Conventional treatments and its disadvantages

Surgery, external radiation therapy, radiosurgery, chemotherapy, targeted treatments, immunotherapy and palliative therapy alone or in combination are the strategies used to treat lung cancer [5]. The type of strategy depends on the stage and type of lung cancer, length of treatment and a person's health history. Cisplatin, Carboplatin and other platinum-based chemotherapeutics, paclitaxel (PTX) and gemcitabine (GCB) are commonly used in traditional chemotherapy [5]. Targeted therapeutic drugs, which can specifically attack cancer cells based on the receptors present on the surface, include Erlotinib and Afatinib [6].

The most recent chemotherapeutic drug, pembrolizumab (commonly known as Keytruda) is gaining popularity for the treatment of lung cancer. Keytruda is a monoclonal antibody against immunoglobin IgG-4-κ isotype which blocks the activity of programmed death receptor-1 (PD-1) and reactivates suppressed immune cells to kill tumor cells [7]. Several clinical trials of KEYNOTE series have been conducted to show that this drug has an important role in treatment of advanced lung cancer stages. Although Keytruda is said to be a cost-effective option compared to platinum-based therapeutics, it still costs around $9000 for 200mg which has to be repeated every three weeks [8]. Projecting for a year, this drug will cost more than $1 million, a price which is not affordable to all.

Drug repurposing

Drug repurposing is an exciting new area of study which can be employed to increase the range of economical drugs available for cancer treatment. In drug repurposing, new therapeutic evidence for already licensed drugs are identified or drugs for treating specific diseases are re-investigated for potential efficacy for other conditions [9]. Drug repurposing has many advantages over development of a completely new drug – 1. The repurposed drug has a high safety index since it has already cleared Food and Drug Administration (FDA) approved preclinical and clinical trials. If it has been declared safe for commercialization, the drug is less likely to fail in upcoming safety trials, 2. The repurposed drug will have a reduced time frame, as many intermediate steps like drug synthesis, preclinical testing and safety assessment could have been completed already. The time taken for traditional drug development is 12-16 years whereas it is only 6-8 years for repurposed drugs (Figure 1), 3. Lower investments are required to test the drug and commercialize it (Figure 1) and 4. New targets may be revealed by the mechanism of the repurposed drug and their pathways can be further exploited [10].

Drug repurposing strategy

Drug repurposing requires intensive background research of

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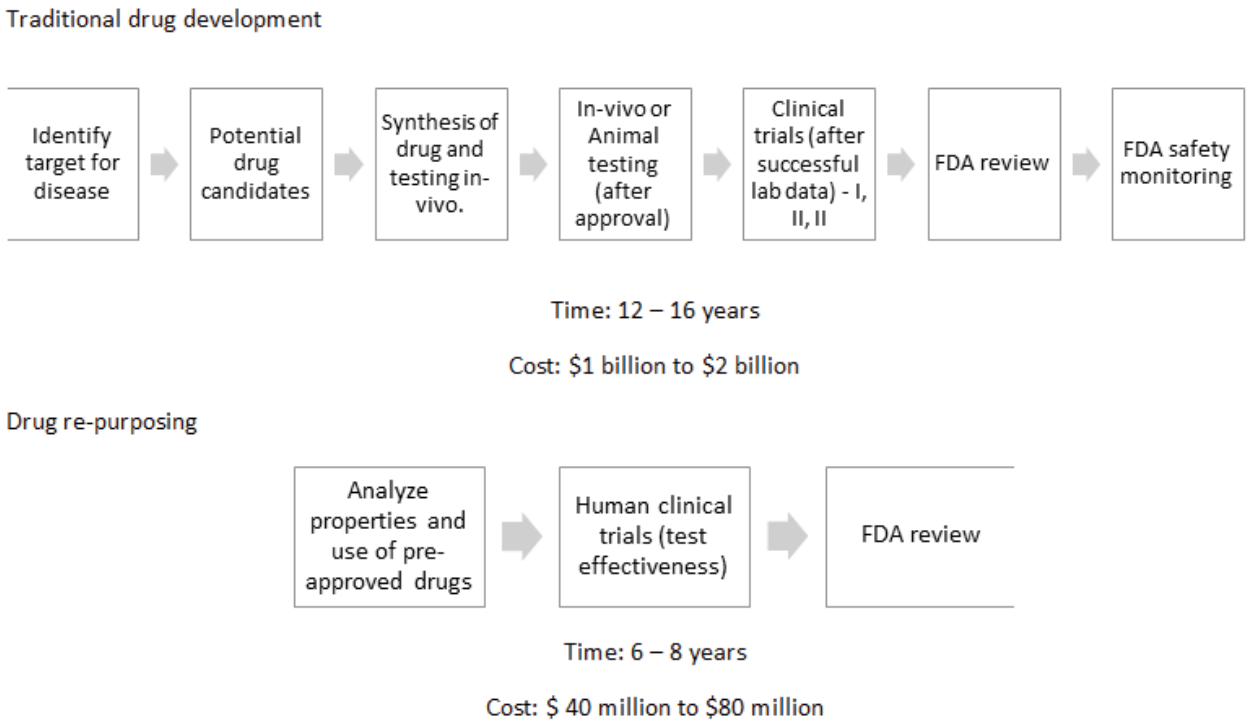

Figure 1: Difference between traditional drug discovery and drug re-purposing [11,12].

the drug and a comprehensive understanding of genomics and the molecular pathways in humans. This process is simplified with the utilization of *in silico* screening methods of small molecule libraries. Multiple online databases such as CMap, Drug Bank, KinaseMap, PharmGKB and cBioPortal are often used to find repurposed drugs with the necessary target [11,12]. These databases are generated by collecting information from various studies based on expression of drugs on human cells. The strategy follows three basic steps: 1) Query input in chosen online portal, 2) Pattern-matching against agents in database to find shared mechanisms of action or mimicry and 3) Output consisting of similar acting molecules [13]. *In vitro* studies are performed to validate the output. After identification of the candidate drug, the next stage involves evaluation of drug effect in pre-clinical trials and assessment of efficacy in clinical trials [14].

Literature Review

This review explores four classes of drugs which were initially identified as: antibiotics, anti-depressants, anti-psychotics and anti-parasitic; and their effect on lung cancer. These drugs have off-targets – meaning that the drug has biological activities other than the intended target for which the drug was commercialized for – which can be selected for antitumor activities. This review also discusses about the synergistic effects of combinations of drugs. Combinations of drugs are especially useful in cancer as tumor growth is driven by multiple intracellular pathways and inhibition of one pathway is not enough to impair the growth. The selected candidates have to be experimentally tested *in vitro* and *in vivo* to validate the protective effects of the drug against the new disease [15].

Antibiotics

Tigecycline: Tigecycline (TGI) is an FDA-approved drug which is used to treat abdominal and skin infections by inhibiting the protein synthesis process in bacteria [16]. Previous research has shown that TGI selectively kills leukemic cells without affecting normal blood cells [17]. A study performed by Jia et al. showed that TGI dose-dependently inhibited proliferation by selectively inducing apoptosis in non-small cell lung cancer (NSCLC) cells over normal human fibroblast cells *in vitro* and *in vivo*. The study also showed a decrease in mitochondrial membrane potential, low mitochondrial respiration, reduction in ATP levels and increased ROS levels [17]. This suggests that TGI inhibits the mitochondrial metabolism of NSCLC cells which is a primary source of energy for cancer cells. Clinical trials for TGI are currently in phase II with phase I trials showing relative safety and tolerance apart from mild gastrointestinal events [16]. Similar drugs which target mitochondrial metabolism can also be a potential therapeutic strategy for NSCLC.

Ceftriaxone: A third-generation cephalosporin, Ceftriaxone is FDA approved and used to treat bacterial infections such as pneumonia, meningitis and gonorrhea [17,18]. Ceftriaxone has a structure that is similar to Ceftiofur – a drug proven to have potential anti-tumor activities [19]. Previous studies have shown that Aurora B, a serine/threonine kinase which regulates mitosis events such as chromosome alignment and cytokinesis, is highly expressed in lung cancer cells [20]. In the study, this kinase appears to be a secondary-target for Ceftriaxone. The antibiotic specifically binds to Aurora B and inhibits anchorage independent growth of lung cancer in both *in vitro* and *in vivo* models by allowing chromosome abnormalities and subsequent cell arrest or apoptosis [18]. Another study with 192 lung cancer patients reported that Ceftriaxone was well tolerated, with no allergic reactions. The drug was shown to be cost-effective for routine use [21].

Anti-depressants

Sertraline and Fluphenazine: Sertraline and Fluphenazine are anti-depressant drugs chosen as candidates by *in silico* methods. This computational approach involved the construction a DGI (drug-gene

interaction) network and GDN (gene-disease association network) which integrated information from various public databases such as DrugBank, PharmGKB, TTD (therapeutic target database), OMIM and CTD (comparative toxicogenomic database). Statistical methods such as Fishers exact test and Benjamini-Hochberg method were used to predict drug-disease association pairs. Out of the 95 predictions, the two anti-depressant drugs were top ranked [22].

Sertraline showed more cytotoxicity and was thus chosen as a potential anti-cancer agent. The synergistic effects of sertraline with a chemotherapeutic drug erlotinib was studied. It was found that sertraline increased erlotinib-induced autophagy specifically in NSCLC cells and not in normal cells. Data showed that sertraline inhibited the mTOR cell growth signaling pathway by blocking phosphorylation of mTOR and accelerated the AMPK energy maintenance pathway by increasing AMPK phosphorylation [22]. Based on the evidence, this combination has the potential to treat NSCLC and needs to be studied further with preclinical and clinical trials.

Imipramine and Promethazine: A bioinformatics approach was used by a study to identify candidates from the U.S. Food and Drug administration (FDA)-approved list for agents that may affect the SCLC gene expression signature [23]. The candidates selected were tricyclic anti-depressant (TCA) molecules which are inhibitors of G-protein Coupled Receptors (GPCR): Imipramine – which is used for depression and Promethazine – which treats motion sickness and is also used as a sedative [24]. These candidate drugs were found to reduce tumor size without forming any large lesions (even in chemo-resistant tumors). Both the drugs were also found to induce apoptosis only in small-cell lung cancer (SCLC) but not in NSCLC cells. This specificity may be due to the presence of G-protein coupled receptor (GPCR) on the surface of SCLC cells. It was suggested that inhibition of GPCR results in inhibition of the PKA cell growth pathway, although more experiments are required to investigate it [23].

On the basis of observation from the study, it was concluded that tri-cyclic antidepressants are best used in second line of therapy as a majority of the SCLC tumors may be at least partially responsive to TCA. Clinical trials are required to validate these preclinical findings [23].

Anti-psychotics

Trifluoperazine: Trifluoperazine (TFP) was identified as a candidate through an in-silico method called Connectivity Map (CMap) [25]. CMap is an online portal that stores thousands of cellular signatures derived from human cells and studies the connection between genetic alterations, disease states and drug actions [13]. It employs rank-based, non-parametric pattern matching to find molecules that mimic the query compound. Using a cancer stem-like cell (CSC) gene signature as input, CMap generated a list of candidates. After further refining, the study selected an anti-psychotic drug, TFP [25] as a potential candidate for CSC inhibition. CSC contributes to tumor initiation, distant metastasis, drug resistance acquisition and disease recurrence and hence, targeting CSCs provides a new strategy for treatment of cancer [26].

In this study, TFP was seen to suppress tumor sphere formation is NSCLC type of lung cancer. The anti-CSC properties of the drug corresponds to the decreased expression of Wnt/β-catenin signaling pathway and suppression of c-Myc oncogene. Combination of TFP with chemotherapeutic drugs such as gefitinib and cisplatin showed reduced cell viability and enhanced apoptotic activity [25]. Phase 1 clinical trial using TFP in combination with bleomycin showed safe toxicity profiles, but further evaluation on the efficacy of the drug is required [27].

Penfluridol: Penfluridol is an anti-psychotic drug used to treat patients with schizophrenia. Recent research has evaluated the anti-tumor properties of Penfluridol in breast and pancreatic cancer [28,29]. A study indicated that the drug induces non-apoptotic cell death through accumulation of autophagosomes in lung cancer cells too. The results showed the upregulation of LC3 by penfluridol which corresponds to increased autophagosome synthesis and an increase in p62 (autophagy specific substrate) by penfluridol, which blocks lysosomal degradation in the cytosol. This causes an accumulation of autophagosomes which in turn increase ROS levels and depletes energy and ultimately, induces cell toxicity [30]. These findings strongly support penfluridol as a repurposed drug for treating NSCLC, especially for the cancer types that are resistant to chemotherapy and will benefit from further clinical trials.

Anti-parasitics

Potassium antimonyl tartrate: Potassium Antimonyl Tartrate (PAT) – An anti-parasitic drug, was identified by screening the U.S. Food and Drug Administration-approved chemical drugs against tumor angiogenesis in NSCLC cells [31]. To validate this result, i*n vitro* and *in vivo* experimental assays were conducted which showed that this drug has anti-angiogenic and tumor reducing properties in NSCLC-specific cells. Evaluation of phosphorylation status of tyrosine kinase receptors indicated that PAT can inhibit many important receptor kinases involved in angiogenesis. The principle targets, however, are cell motility and differentiation. This can be seen by the repression of Src/FAK signaling pathway which in turn, downregulates receptors involved in cellular growth [31]. Although PAT was abandoned as a treatment option for leishmaniasis due to its toxicity [32], preclinical trials reported to be clinically safe due to much lower concentrations of PAT used.

Mebendazole: Mebendazole (MBZ) is an anti-helminthic drug used to treat parasitical worm infections. It is also known to have anti-angiogenic action which has been shown to inhibit growth of certain cancers [33,34]. MBZ also has slight activity against mammalian tubulin [35]. The apoptotic response to microtubule disruption is mediated by Bcl-2 phosphorylation [36]. The primary recognized mechanism of action, however, is inhibition of neovascularization, which validates previous findings of anti-angiogenic property of MBZ [35]. The study reported that this drug would be more effective in combination with other drugs or treatment modalities [36]. Although this drug is currently undergoing human clinical trials for various cancers, *in-vitro* and *in-vivo* models have indicated therapeutic potential.

Discussion and Conclusion

Drug repurposing is gaining attention in lung cancer research as it helps to develop more economical chemotherapeutic drugs. It also increases the number of effective drugs against lung cancer in the market as there is an urgent need to find new drugs without conferring resistance to the drug. The drug repurposing approach employs *in silico* tools to obtain novel secondary molecular targets of pre-existing medications which can be used to halt cancer development. Four classes of drugs were discussed in this review and in each, the candidate drug was chosen either using online databases or from previous research. *In vitro* studies were performed to validate the secondary target of the drug and to determine the mechanism of action by which tumor progression is inhibited.

Drug repurposing has many advantages. However, there are a few challenges too: The approved non-cancer drugs cannot be tested blindly in cancer patients without valid mechanistic in- sight into their possible efficacy. It is also uncertain whether drug doses, formulations, and routes of administration similar to those used for the original indication are needed for a new anticancer indication.

These challenges can be overcome by performing extensive studies on the safety of repurposed drugs with different dosing and ethnic populations. Experiments using compatible combinations of drugs should also be carried out as they bear a higher chance to terminate cancer progression. Development in the field of drug repurposing requires a need for better integrative platforms for data analysis. Compounds are tested in different laboratories around the world and thus, access to experimental, preclinical and clinical data from these industries will be useful for confirmation and to avoid repeats. This will ensure a more collaborative approach which will ultimately obtain results in a shorter period of time. Lastly, there is also a need for funding opportunities for repurposing initiatives. Despite these challenges, drug repurposing for anti-cancer therapy, as discussed in this review, is a very good strategy for development of potential chemotherapeutic drugs.

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