ScienceDirect

European Journal of Pharmacology

Volume 866, 5 January 2020, 172784

Review

Old wine in new bottles: Drug repurposing in oncology

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Received 10 July 2019, Revised 5 November 2019, Accepted 7 November 2019, Available online 12 November 2019, Version of Record 12 December 2019.

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https://doi.org/10.1016/j.ejphar.2019.172784

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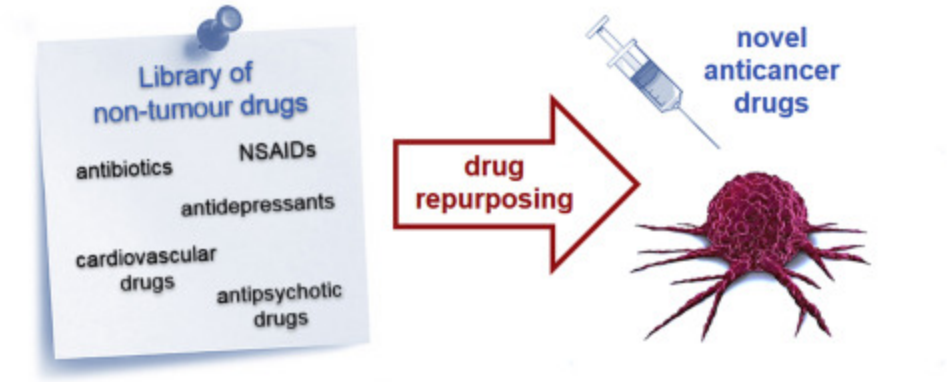
Abstract

Increasing costs, much time consumption and high risk of failure associated with the process of *de novo* development of new anticancer drugs have prompted the pharmaceutical

industry to seek alternative strategies that may facilitate and accelerate the whole process. In particular, the repurposing strategy, known also as repositioning or reprofiling strategy, is a potential source of new treatment options for cancer patients with high unmet medical needs. However, it should be noted that the repurposing strategy, being still a new trend in drug development, should only complement the process of discovering new anticancer drugs, and should not be its alternative. The best repurposable oncological drug candidates are the agents whose original patent protection has already expired, and for which there is a possibility to create a formulation enabling, together with a new therapeutic indication, new patent protection. In this review article we discuss the advantages of the repurposing strategy, and provide an overview of a number of promising candidates, such as artesunate, aspirin, cimetidine, doxycycline, ivermectin, metformin, rapamycin (sirolimus), and thalidomide, that have the potential to be repurposed as anticancer drugs both in cancer prevention and therapy. In addition, we highlight some of the studies regarding the signalling pathways and molecular targets altered by these drugs, and describe the biological mechanisms underlying their anticancer effects.

Graphical abstract



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Introduction

Although oncological medicine has had several milestones in the fight against cancer, the cancer patients are still waiting for development of both effective and tumour-specific therapies. Conventional chemotherapy relies on the premise that intensively proliferating tumour cells should be more likely killed by chemotherapeutic agents than normal cells (Seitz et al., 2013). However, in reality, currently used cytotoxic drugs have only little or no

specificity, which leads to poor response to therapy applied, that finally results in different dose-limiting side effects (Huang et al., 2017). Besides, cancer patients usually have impaired immune system, and thus are particularly vulnerable to all types of infections, including bacterial and parasitic ones (The Center for Disease Dynamics, Economics & Policy – reports, 2016).

As far as economy is concerned, cancer is the cause of a decrease in labour resources and reduction of its productivity, as well as elimination of some people from the labour market in case of disability and premature death (Bates et al., 2018). This may lead to two types of consequences: (i) the income of the sick households and their informal care givers decreases, which leads to a reduction in consumption and investment spending; and (ii) the output of companies decreases. Of course, the replacement and hiring of new workers, if possible, will over time lead to recovering the initial output. This does not change the fact that the production that would have been made by the ill person if he had not become sick was not made, and the related loss adds to the costs of the disease to both the economy and society. Limited production translates into lower incomes, household expenditures, social contributions paid by them, and thus leads to deterioration of public finances. Finally, cancer affects the budget not only by reducing the contributions to it, but also by increased spending on patients in the form of rehabilitation benefits, sick benefits, and pensions.

In the context of both social and economic aspects of cancers mentioned above, extensive efforts have been made to develop novel and highly efficacious tumour-targeting agents to overcome the shortcomings of conventionally used chemotherapeutics. To this end, natural products and their (semi)synthetic derivatives remain an important source of leads and inspiration (Rayan et al., 2017; Iqbal et al., 2017).

Unfortunately, for many years, a steady upward trend in the prices of oncological treatment has been clearly observed (Prasad and Mailankody, 2017). The anticancer chemotherapeutics routinely priced at more than $100,000 per year of treatment (Mailankody and Prasad, 2015), and some of them nearing even the threshold of $200,000 per year. It has an extremely negative impact on both the economy and society, particularly on cancer patients. On the other hand, it has been found that the median cost of *de novo* developing a single anticancer drug is about $650 million (Prasad and Mailankody, 2017). Although a significant increase in the funding for development of new anticancer drugs is observed, the number of the FDA (The Food and Drug Administration) approved drugs for oncology is only ~10–20 each year (Fig. 1) (CenterWatch data, 2019).

Section snippets

Drug repurposing in oncology

There is a growing recognition of the fact that the budgets of most national healthcare services will be unable to further support the increase trend in costs of new oncological drugs for much longer (Bertolini et al., 2015). For example, the worldwide spend on such drugs in 2013 was $91 billion, with global sales of the 10 biggest selling oncology drugs reaching $43 billion.

In the light of these reports, a very promising strategy is the use of drugs already registered in new medical …

Conclusions

Over the years, cancer patients have gained access to new methods of oncological treatment. Apart from the widely used surgical treatment, chemotherapy and radiotherapy, some alternative methods, like immunotherapy, are currently of increasing importance. Many oncologists rely on the standards (schemes) of care, so on the specific therapy guidelines developed in such a way as to guarantee the best results for the majority of patients with a given type of cancer. When creating these patterns, …

Declaration of competing interest

The authors of this review article have no conflict of interest to declare. …

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> …In addition to optimizing therapies for specific cancer patient groups, which includes selection of the right type of statin, and assessing ideal duration and 'window of opportunity' of treatment, determining if single or combined therapy is best will be necessary in the design of future randomized clinical trials. Similar to statins, there are examples of other drug classes that were initially developed for other purposes and show beneficial anticancer effects during sustained and long-term use; these include aspirin (especially in CRC) [224], metformin [225,226], anti-androgens [227], and several others [228]. Although existing ex vivo, animal model and non-randomized data on the anti-cancer effects of statins are promising, long-term clinical trials and results are necessary to evaluate and conclusively establish their therapeutic efficacy.…

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Repurposing old drugs to fight multidrug resistant cancers

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> ...This occurs because repositioning candidates have often been through several stages of development, including efficacy, pharmacokinetics, pharmacodynamics and toxicity, and may even be marketed entities (Fig. 1). The repurposing of drugs has been applied in several chemotherapeutic strategies to treat human health disorders such as cancer (Antoszczak et al., 2020; Armando et al., 2020; Masuda et al., 2020; Mudduluru et al., 2016; Nowak-Sliwinska et al., 2019; Serafin et al., 2019), neurodegenerative diseases (Corbett et al., 2015; De Castro et al., 2018), neglected tropical diseases (Andrade et al., 2019; Sbaraglini et al., 2016), autoimmune diseases (Grammer and Lipsky, 2017), asthma (Huo and Zhang, 2018), psoriasis (Xu and Zhang, 2017), cystic fibrosis (Valeria et al., 2019), and systemic lupus erythematosus (Grammer et al., 2016), to mention a few. With the development of computational methods and the increasing availability of novel types of big data (Kwon et al., 2019), the major limitation to find a new indication of a known drug lays in the identification of the molecular target of the disease of interest....

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