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# Old drugs, novel ways out: Drug resistance toward cytotoxic chemotherapeutics

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ABSTRACT

Efficacy of chemotherapy in the treatment of distinct malignancies is often hampered by drug resistance arising in the tumor. Understanding the molecular basis of drug resistance and translating this knowledge into personalized treatment decisions can enhance therapeutic efficacy and even curative outcome. Over the years, multiple drug resistance mechanisms have been identified that enable tumors to cope with the damage instigated by a specific drug or group of anti-tumor agents. Here we provide an overview of the molecular pathways leading to resistance against conventional anti-cancer drugs, with emphasis on the utility of these pathways for rational selection of treatments for individual cancer patients. We further complement the review by discussing the pitfalls and difficulties in translating these findings into novel treatment strategies for cancer patients.



## 1. Introduction

Conventional chemotherapy is a major arm of anti-cancer therapy, but its effectiveness is often hampered by intrinsic, as well as acquired drug resistance (Assaraf, 2007; Gonen and Assaraf, 2012; Szakacs et al., 2006). Understanding the resistance mechanisms for the different chemotherapeutic agents is crucial to develop better treatment strategies, ideally leading to a personalized drug regimen for better treatment responses, as well as preventing treatment with *a priori* ineffective drugs (Livney and Assaraf, 2013; Shapira et al., 2011). Over the years ample evidence has delineated a multitude of drug resistance mechanisms, both general multi-drug resistance factors and factors specific for one class of drugs. Most of these mechanisms were initially discovered in tumor cell lines, and some have subsequently been validated in the clinical setting. Yet, few, if any, such defined factors are actually used in the clinic as prognostic markers to select the appropriate individual cancer patient's treatment regimen for conventional chemotherapy.

On the other hand, personalized medicine is used successfully for targeted drugs. The evolution of genomic, transcriptomic, proteomic and screening tools has yielded extensive knowledge about the molecular basis driving growth of individual tumors. Based on this information, drugs have been developed that specifically target a protein or pathway that is activated in the tumor. These are often activated kinases such as EGFR in lung cancer, BRAF in melanoma and FLT3 in AML patients (Holohan et al., 2013; Zarrinkar et al., 2009). Alternatively, targeted drugs instigate cytotoxic activity specifically in the context of a tumor-specific mutation, a concept known as synthetic lethality. This is exemplified by the usage of PARP-inhibitors for BRCA1/BRCA2 mutant tumors (Farmer et al., 2005). These targeted drugs often present limited side effects compared to conventional chemotherapeutics and can be effective during the initial treatment responses for these subset of tumors harboring these specific mutations. In addition, genomic instability and consequent tumor heterogeneity often allow cells to acquire drug resistance, by mutations in the drug target or activation of alternative signaling pathways, ultimately yielding acquired resistance and a poor prognosis (Edwards et al., 2008; Smith et al., 2012).

Though conventional chemotherapeutic drugs also include anti-tumor agents with a molecularly defined target (such as the antifolates) (Gonen and Assaraf, 2012), most drugs target essential cellular pathways that are also critical for a tumor. This does not imply that conventional chemotherapeutic drugs are spared from drug resistance, but merely that drug resistance is often

*Abbreviations:* NSLC, non-small cell lung cancer; SNP, single-nucleotide polymorphism.

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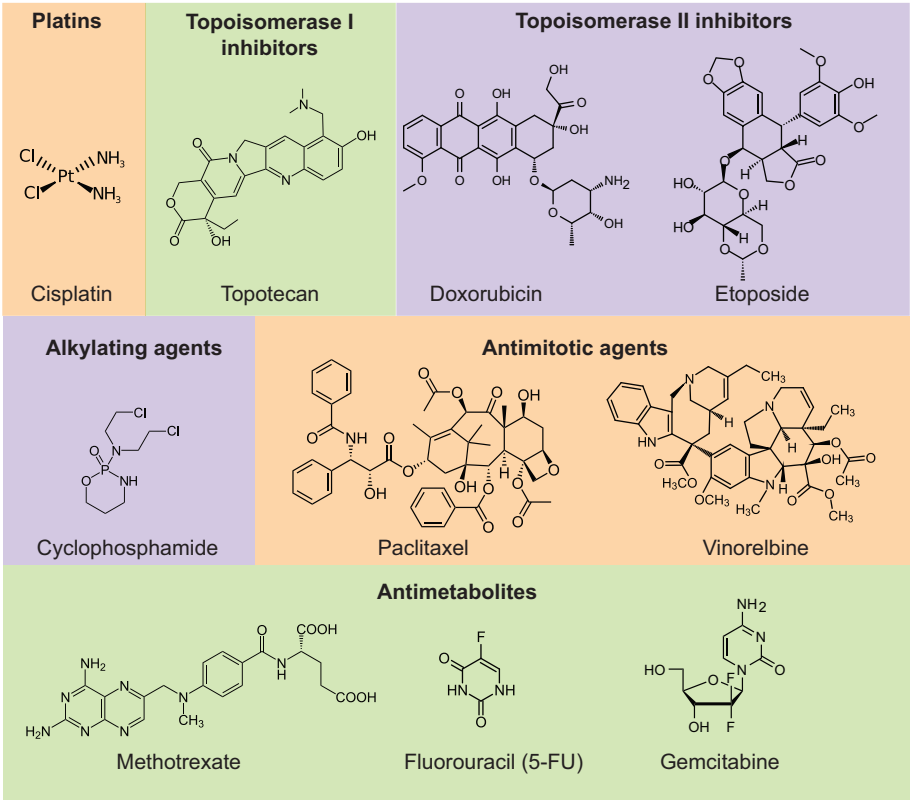


**Fig. 1.** Chemical structures of members of the different classes of chemotherapeutics. Six different chemotherapy classes are distinguished, some of which are divided into several subclasses. For every subclass, the structure of the most commonly used drug is shown.

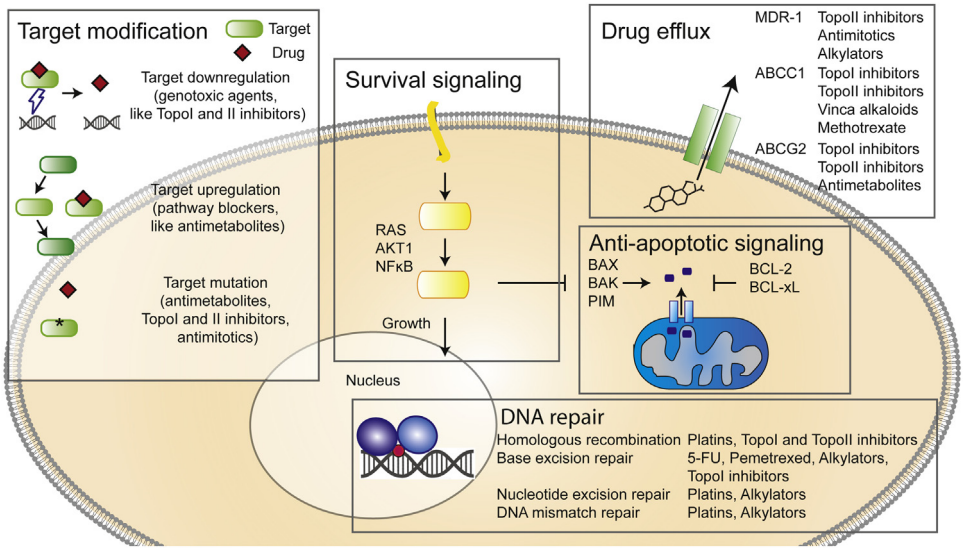


**Fig. 2.** Common cell-intrinsic resistance mechanisms to chemotherapeutics. Cancer cells can become generally resistant to chemotherapeutics by inhibiting the apoptotic pathway or constitutive activation of growth signaling pathways, which also inhibit apoptosis. Alternatively, the expression of drug transporters is upregulated, leading to resistance to a subset of drugs (as indicated). Cells also activate DNA damage repair pathways to cope with genotoxic stress induced by several chemotherapeutics. To avoid effective target inhibition, cells can mutate the drug target, upregulate its expression (in case of pathways blockers, as to prevent full inhibition of the total enzyme pool), or downregulate its expression (for genotoxic agents, to prevent harmful targeting by the drug).

multifactorial. Given the strong untoward side effects associated with most chemotherapeutics, drug resistance not only limits the therapeutic efficacy but also exposes patients to serious toxicity in healthy tissues. Resistance mechanisms toward the different chemotherapeutic drug classes (Fig. 1) have been extensively studied, both in tumor cell lines and in mouse models. Major mechanisms include enhanced drug efflux by multidrug efflux transporters of the ABC superfamily, chemical modifications of drugs into non-effective metabolites, down-regulation of the major drug target, or bypassing the inhibited signaling pathway (Fig. 2). Only a few of these mechanisms have been shown to be operational outside the laboratory setting (i.e. in patients) and the translation of the fundamental understanding of drug resistance mechanisms into clinical practice has not been very successful. However, the