

Variations Related to Resistance of Cancer Cells to Topoisomerase II Alpha Inhibitory Drugs

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Mini Review

Volume 2 Issue 1

Received Date: December 25, 2017

Published Date: February 20, 2018

Abstract

DNA topoisomerase II alpha (Top2- α) enzyme is an important target for many anticancer drugs. A variety of *TOP2A* genomic variants has been found associated with the development of drug resistance to this enzyme, resulting in chemotherapy resistance. Chemotherapy resistance is the ability of cancer cells to survive and grow despite anti-cancer therapies. Increasing information show that genomic variations such as mutations and polymorphisms play an important role in chemotherapy resistance. Here, the available information on mutations that affect the response of Top2- α to its inhibitory drugs was reviewed.

Keywords: Top2- α ; Chemotherapy; Mutation; Resistance

Introduction

Chemotherapy resistance is the multiple drug resistance of cancerous cells. Cancer cells can become resistant to multiple drugs by various mechanisms, such as altered membrane transport, enhanced DNA repair, apoptotic pathway defects, alteration of target molecules, protein and pathway mechanisms [1,2]. As Topoisomerase II α (Top2- α) is an important target for many anti-cancer drugs, variations in this enzyme may influence drug responses in different populations. Top2- α is an intracellular enzyme with the ability to modify the topology of double-stranded DNA during replication and transcription. Top2- α forms a covalent complex with DNA, but in the presence of topoisomerase poisons the breakage-rejoining reaction is interfered with and the topoisomerase II α -DNA complex becomes stabilized, which is lethal to the cell [3].

Top2- α Inhibitor Drugs

Generally, drugs targeting Top2- α can be classified into two groups. The first class of these drugs is Top2- α inhibitors that target the N-terminal ATPase domain of the enzyme, and inhibit the enzyme from turning over [4,5]. The second class of the drugs persuades the forward cleavage reaction or prevents the re-ligation of DNA [6-8]. Despite the widely application of Top2- α inhibitors in the treatment of cancer, several mechanisms has shown to cause drug resistance [9]. A variety of mutations in this gene have been associated with the development of drug resistance [10-13].

Top2- α Variations Related to Drug Resistance

Several studies have shown that mutations that reduce

the catalytic activity of Top2, and mutations in the residues participating in DNA-binding as well as the

mutations in the drug-binding pocket could result in Top2- α drug resistance (Table 1) [9,10,14-18].

Compound Name	Miss-sense Mutation	Reference
Amsacrine	Arg487Lys	Hinds, et al. 1991 [11]
	Arg450Gln and Pro803Ser	Mao, et al. 1999 [19]
	Glu571Lys and Arg486Lys	Patel, et al. 2000 and Sader et al. 2017 [20,21]
	Lys529Glu, Arg568His, Arg568Gly and Thr530Met	Farsani, et al. 2017 [22]
Teniposide	Arg449Gln	Bugg, et al. 1991 [10]
	Arg450Gln and Pro803Ser	Mao, et al. 1999 [19]
Etoposide	Arg487Lys, Lys798Asn and Pro803Ser	Patel, et al. 1993 and Danks et al.1993 [12,13]
	Deletion of Ala429	Campain, et al. 1994 [18]
Doxorubicin	Arg450Gln and Pro803Ser	Mao, et al. 1999 [19]
Bisdioxopiperazines	Thr49Ile, Tyr50Phe, Lys162Gln and Leu169Phe	Campain, et al. 1994 and Larsen et al. 2003 [17,18]
Mitoxantrone	Arg450Gln and Pro803Ser	Mao, et al. 1999 [19]
	Arg487Lys and Tyr481Cys	Farsani, et al. 2017 [22]

Table 1: Top2- α variations related to drug resistance

In 1991, Hinds *et al.* showed that genomic variation changing Arg487 to Lys (R487K) could confer >100-fold resistance to Amsacrine [11]. Moreover, Bugg, et al. reported that R449Q variation in Top2- α causes Teniposide resistance [10]. In 1993, it was shown that R487K, K798N and P803S are the main cause of Etoposide resistance [12,13]. In 1994, Campain, et al. reported that a 3 bp deletion of nucleotide 1320-1322, resulting in a deletion of Ala429 in Top2- α , presents in Etoposide resistant human melanoma cell lines [18]. Mao, et al. in 1999 identified two mutations, R450Q and P803S, in the coding region of the human topoisomerase II α gene in the atypical multidrug resistant (at-MDR) cell line, CEM/VM-1, which exhibits resistance to many structurally diverse topoisomerase II-targeting antitumor drugs such as Teniposide Doxorubicin, Amsacrine and Mitoxantrone. They showed that both R450Q and P803S mutations confer resistance in the absence of ATP. However, in the presence of ATP, the R450Q, but not the P803S, mutation can confer multidrug resistance [19]. In 2000, Patel *et al.* showed that single point changes of Glu571 to Lys (E571K) or Arg486 to Lys (R486K) in the human topoisomerase II α , could be shown *in vivo* to confer >25-fold and >100-fold resistance, respectively, to Amsacrine [20]. Sader, et al. in 2017 by using molecular dynamics simulations indicated that there is a significant impairment of Amsacrine binding energy in E571K and R486K mutants compared with the wild type [21]. It was also documented that T49I, Tyr50Phe, K162Q, and L169F mutations could cause Bisdioxopiperazines resistance [17,23].

Recently, we computationally examined the mechanisms by which nsSNP variations in Top2- α could affect its response to Amsacrine and Mitoxantrone as important inhibitors of the enzyme. The results of the study showed that K529E, R568H, R568G and T530M variations could significantly affect the position and binding energy of Amsacrine in Top2- α , which could mediate resistance of this polymorphism to Amsacrine. Moreover, R487K and Y481C variants could change the response of the enzyme to Mitoxantrone [22,24].

As treatment with Top2 poisons is usually associated with an increased risk of secondary malignancies and cardio-toxicity [25,26]. Therefore, it is very important to know whether the drug could have effective treatment function. With this purpose, study of the mutations related to chemotherapy resistance could be very informative and improve cancer treatment.

Acknowledgment

This study was supported by department of research of University of Isfahan, Isfahan, IR Iran. The authors declare that there is no conflict of interest.

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