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Review Article

Mitoxantrones for Cancer Treatment and there Side Effects

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Submitted: 02 December 2016

Accepted: 01 February 2017

Published: 02 February 2017

ISSN: 2379-9498

Keywords

- Mitoxantrone
- Anticancer activities
- Topoisomerase II
- Cardiac toxicity
- Analogues

Abstract

Mitoxantrone is an anticancer drug which is mostly used for the treatment of breast cancer and non-Hodgkin's lymphoma. Its structure is related to anthracycline. There are only few methods available for its synthesis. It is synthesized to reduce the cytotoxic effects of anthracycline derivatives. There are more than fifteen analogues of mitoxantroneon the basis of different groups attached at positions 1 to 4. It is an inhibitor of DNA-topoisomerase II, but its exact mode of action is unknown. The spectral elucidation and elevation of melting temperature technique are used to study DNA-binding properties of mitoxantrone. The major adverse effects of mitoxantrone usage arecardiotoxcityand effecting the electron transport chain in mitochondria. Efforts are required to synthesize better analogues of mitoxantrone that posses cancer cell specific cytotoxicity.

ABBREVIATIONS

MX: Mitoxantrone; DNA: Deoxyribonucleic Acid; Ssdna: Single Stranded Deoxyribonucleic Acid; Dsdna: Double Stranded Deoxyribonucleic Acid; DPV: Differential Pulse Voltammetry ; CV: Cyclic Voltammetry; CPE: Carbon Paste Electrode; RRMS: Relapsing-Remitting MS; PRMS: Progressive Relapsing MS (PRMS); LVFE: Left Ventricular Ejection Fraction; CHF: Congestive Heart Failure; ECG: Electrocardiogram; MX-MET: L-Methionine-Conjugated MX

INTRODUCTION

Mitoxantrone has a wide range of antitumor activities. It can be used to treat various types of malignancieswhich may include breast cancer,non-Hodgkin's lymphoma and acute myeloidleukemia but not the chronic myeloidleukemia.It has been approved as an immune modulatory agent for reducing fourteen different types of worsening relapsing–remitting multiple sclerosis (MS) by U.S Food and drug administration (FDA) [1]. In the year 2000 it has been approved for the treatment of neurologic activities by FDA. It is also used to reduce the rate of clinical regenerations in patients with inferior progressive, progressive degenerating, or worsening degenerating-remitting multiple sclerosis [2].

Mitoxantrone is a semisynthetic anticancer drug having international union of pure and applied chemistry (IUPAC) name of 1,4-dihydroxy-5,8-bis{[2-[(2-hydroxyethyl)amino]-ethyl] amino]-9,10-anthracenedione. It is powerful cytotoxic agent to cure a variety of cancers [3,4]. Mitoxantronestructure (Figure 1) is related to anthracenedione derivative which is structurally related to anthracycline. Theanthracyclines are commonly used for upto 75% chemotherapeutic treatment of cancers [5]. However, the additional hydroxyl groups are present at 5-and 8-positions of mitoxantrone [6]. It has been synthesized to improve the anticancer activity of anthracycline and to reduce side effects of anthracyclines such as cardiotoxcity [1]. It is hydrophobic molecule showing less solubility in water even when it is available in its hydrochloride form [6]. In lipids it shows better solubility as compared to other solvent however it also show solubility in octanol [7,8]. The value of lipid water portioning coefficient of mitoxantroneis calculated to be 23000 and due to this reason it can cross the plasma membrane with high speed [9].

Synthesis

According to US patent number 4197249 (Murdock &Durr

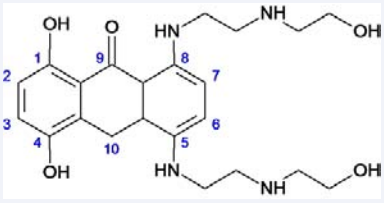

Figure 1 Chemical Structure of Mitoxantrone.

1980) the preparation of mitoxantrone has been done by using leuco-tetrahydroxyanthraquinone as starting material (Figure 2). The general scheme is as under.

However the leuco-tetrahydroxyanthraquinone can be better prepared by the method of Chen et al. This process involves the synthesis of Mitoxantrone in four steps. According to Chang (1992) the syntheses of leuco-tetrahydroxyanthraquinone occur in three steps which are key intermediate for mitoxantrone synthesis. Chrysazin are used as the precursor for this synthesis. In the first step nitration of chrysazin is done in the presence of 20% oleum and ice cooling is required in order to get 4, 5-dinitro-chrysazin (Figure 3). During this process an undesired isomer that is 2, 4-dinitrochrysazin is formed, which reduces the yield. The calculated yield of the desired isomer is 80 %, while 5% is that of undesired isomer. This undesired isomer is removed by recrystallization in DMF-benzene ethanol mixture. In the second step the nitrofunctional group can be reduced by using iron metal in sulfuric acid. In this step, 90% yield of 4, 5-diaminochrysazin was claimed. In the third step diaminochrysazin is converted into leucotetrahydroxyanthraquinone. This intermediate does not require further purification.This compound is considered to be hygroscopic, light and oxygen sensitive according to Chang & Cheng (1995). This compound should be immediately utilized in the of fourth step for product formation [10,11]. Further the synthesis of mitoxantrone from intermediate compound of leucotetrahydroxyanthraquinone was reported by Murdock &Durr [12]. In this step the Schiff base is formed by condensation of leuco-tetrahydroxyanthraquinone intermediate with an amino alcohol (2-(2-aminoehtylamino)-ethanol), which are then

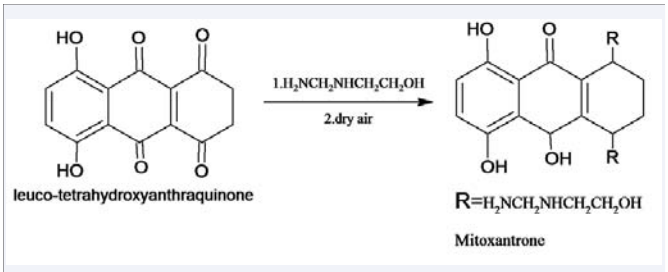

Figure 2 Preparation of mitoxantrone (Murdock &Durr 1980).

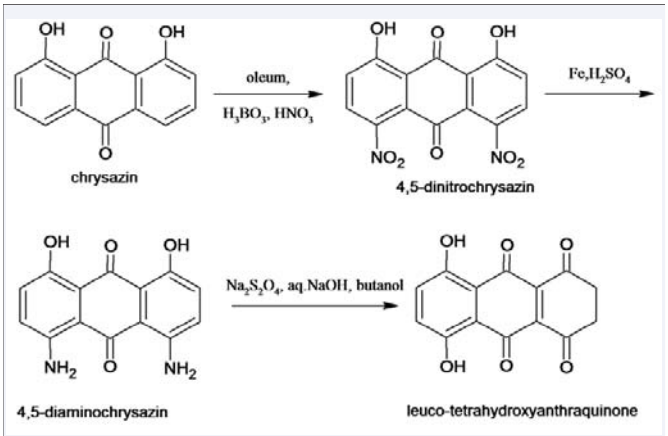

Figure 3 Preparation of leuco-tetramine hydroxyl anthraquinone [10].

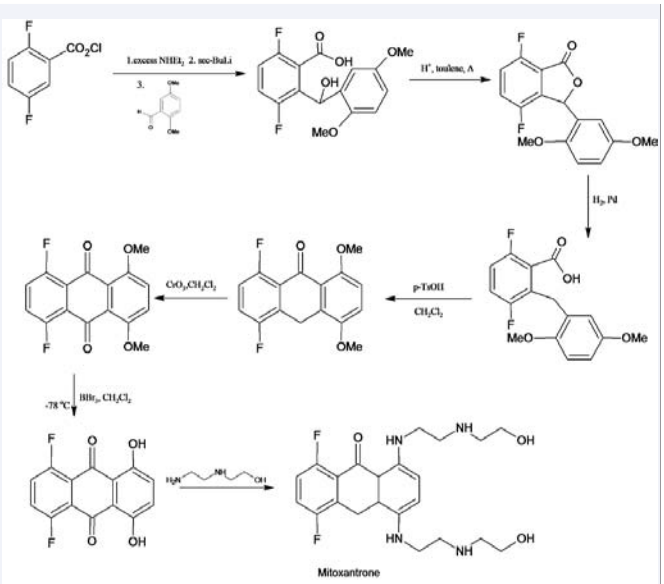

Figure 4 Synthesis of Mitoxantrone [13].

converted to final product of mitoxantrone by oxidation with dry or wet air [12]. This method of synthesis of mitoxantrone was also reported by Krapcho [12]. [13]. The schematic pathways for this synthesis are as follows.This pathway involves more difficult steps in terms of chemical handling such as the use of highly reactive boron tribromide and to handle the highly flammable butyl lithium during ortho-metallation reaction. The initial anthraquinones framework relies on the initial ring formation. The amino alcohol side chain was introduced by nucleophilic displacement of fluorine leaving group (Figure 4) [13].

Analogues of Mitoxantrone

The mitoxantrone has 15 types of analogues which are different on the basis of groups at position No 1, 4,5 and 8, that are R_1, R_2, R_3 and R_4 respectively, (Figure 5). Some of them are described in (Figure 6).

Mode of Action of Mitoxantrone

The cancerous cells growth can be halted through theanthracyclines by two methods. These are

a) Inhibition of topoisomerase [12].

b) By reaction of anthracycline with iron to produce reactive oxygen species [16].

Similarly the mitoxantrone is an inhibitor of DNA-topoisomerase II [17]. The drug can be taken orally or

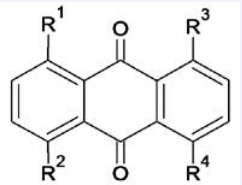

Figure 5 Basic nucleus of mitoxantrone.

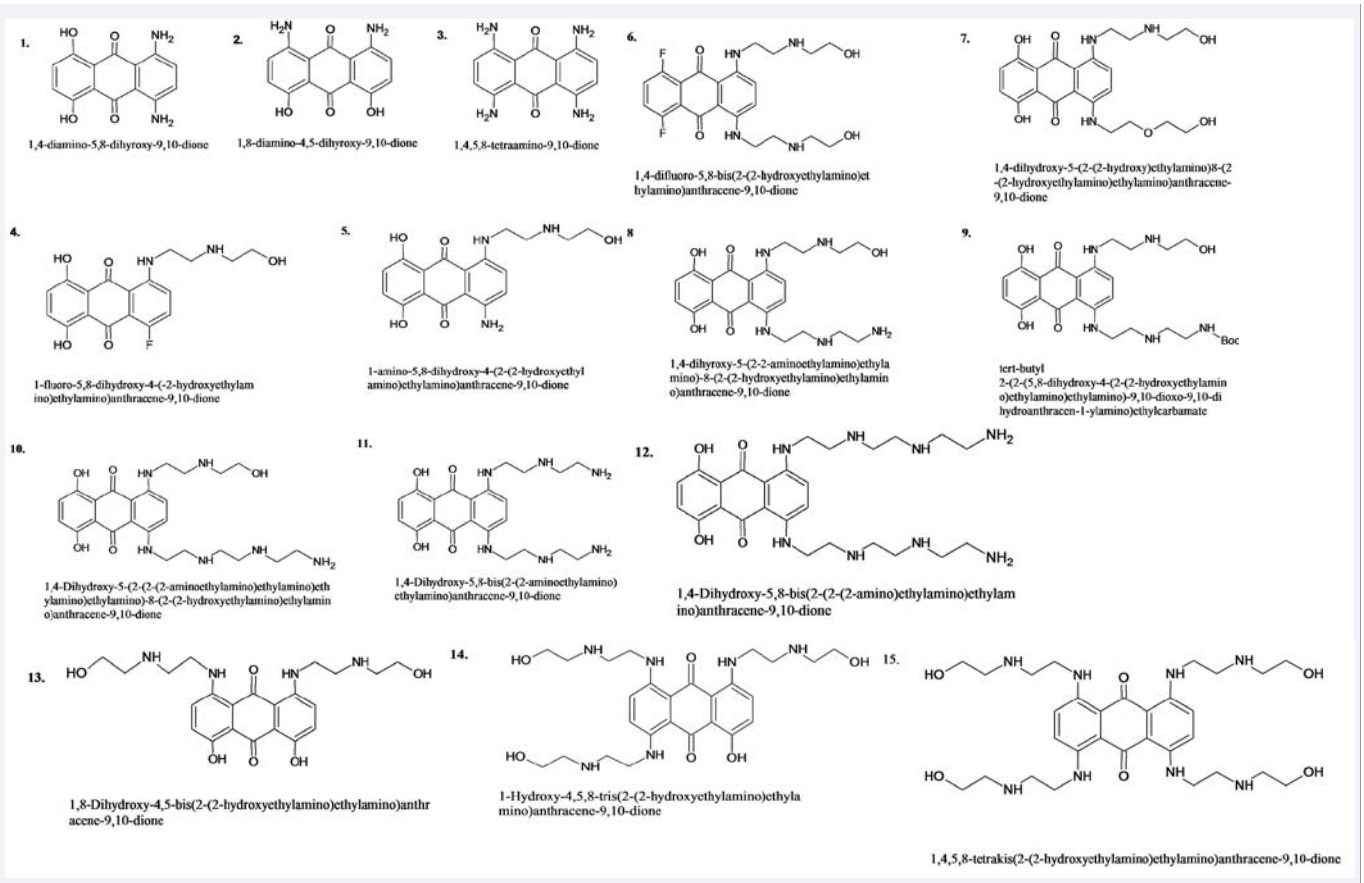

Figure 6 Analogues of Mitoxantrone [14].

intravenously. The target of the drug can be DNA inside the cellnucleus, with which it intercalates halting its replication and RNA transcription and subsequently the protein translation process. DNA binds with small molecules in three different modes: By electrostatic interaction through its negatively charged sugar-phosphate structure or, By binding the drug by interacting through the two grooves of DNA double helix or, Intercalationof drug among stacked base pairs of native DNA. The active site tyrosine of topoisomerase II act as nucleophile, that attack the phosphodiester backbone of DNA and removes the torsion from it. A new termis introduced for the mode of action of topoisomerase inhibitors that inhibit the binding of enzyme with DNA. It is called enzyme poisoning and its function is similar to that of other drugs that perform catalytic inhibition [18]. Wu et al. explain the interaction of Topoisomerase IIβ with MX and, Toposiomrase IIβ crystal structure was determined which was stabilized by MX [19].Leukaemia cell line when treated with mitoxantrone showed down regulation of Top II β thus mitoxantrone form a strong cleavage complex with Top II α in comparison to its cleavage complex with Top II β [20,21]. The mitoxantronehas high affinity to recognize the chromatin structure than the free DNA.Mitoxantrone binds to chromatin to form compact structure which inhibits the extraction of histone protein from drug treated chromatin. However the exact mode of action of mitoxantrone is still not known [22]. The interaction of mitoxantrone was also analyzed through the use of differential pulse voltammetry (DPV) and cyclic voltammetry (CV) at carbon paste electrode (CPE) for its interaction with calf thymus double strand DNA (dsDNA) and calf thymus single stranded DNA (ssDNA).It wasobserved that whenmitoxantrone binds to DNA, resulting achange in mitoxantrone signal showing a decrease in signal intensity which was attributed to the interaction of mitoxantrone with DNA. A change can also be observed in the peak current of oxidation wave of mitoxantrone due to addition of an excess of dsDNA or ssDNA in mitoxantronesolution. Concentration of mitoxantrone has also a remarkable effect on the interaction of mitoxantrone with dsDNA. The response of mitoxantrone increase with concentration sharply in both cases that is in bare and dsDNA modified CPE's.They authors explain the variation of volumetric behavior of mitoxantrone in aqueous medium at DNA modified CPE. This process was done in order to modify promising DNA biosensors for development of new anticancer drug [23]. The interaction of drug DNA complexes was carried out by Ritu et al., who showed that MX interacts with DNA in parallel manner because the energy in this case is one order less than in perpendicular case. The position of base is also change in perpendicular mode of binding. The conformations of side chains near to hydroxyl group are considerably different in two manners. Orientations of the ring system occur at the intercalation site, thus conformation of side chain and DNA depends upon the position of substituent side chain. Thus the structure of the drug, its conjugation with DNA and its anticancer activity all showing the important role of drug designing that can bind tightly with DNA [24]. Foye et al., used the spectral

elucidation and elevation of melting temperature technique to study DNA-binding properties of mitoxantrone. It was observed that mitoxantronecan binds to DNA with the help of two different sites: a) By interactionbetween consecutive base pairs and b) through electrostatic interaction including DNA phosphate group and amino side chain of mitoxantrone drug [25].

The Observed Side Effects

The cardiotoxicity of mitoxantrone depends on two factors, one is age and second is the life time cumulative dose and both of these are important [1]. Nowadays in around 2.6% to 13% patients, increase in cardiac toxicity has been notice with 140 mg/m^2 dose of mitoxantrone which is consider as maximum life time dose [1]. The mitoxantrone can be used in pediatric population which include treatment of cancer and it also increase the survival rate when treated as a second line therapy for multiple sclerosis [26]. According to the data collected by Van Dalen et al, [12], the occurrence of mitoxantrone related cardiotoxicity of clinical heart failure and asymptomatic cardiac damage have different ranges. mitoxantrone-related symptomatic cardiotoxicity/clinical heart failure varies between 0 to 6.7% whereas asymptomatic cardiac damage varies between 0-80% for children under 18 years of age. Studies show the mitoxantroneinduced cardiotoxicity is similar in mechanism to that cause by anthracycline [28,29]. *Invitro* (H9c2 cardiomyoblasts) and *in vivo* (male Wistar rats) studies showed damage to mitochondria and cardiotoxicity due to mitoxantrone [30-32]. The electron transport chain(ETC) is considered as the endpoint for toxicity caused due to mitoxantrone. Incase of study on cardiomyoblasts (H9c2) mild oxidative stress was observed after mitoxantrone treatment and energy imbalance occur due to increase of reactive oxygen species (ROS) in the redox cycle [32]. Incase of mitoxantrone treatment in rats ETC activities was greatly affected and as a result decrease in amount of ATP in mitochondria has been observed [31]. Congestive heart failure was also observed in patient having drug dosage above the 100mg/m^2, that occurs mostly in the patients having more risk factors of cardiac. Also at the concentration of dosage below 100mg/m^2 cardiac dysfunction was observed [33]. Iron transport in mitochondria was done by p-glycoprotein so its function in mediation of mitoxantronecan not be neglected [33]. This drug is approved for treatment of various disease such as worsening relapsing-remitting MS (RRMS), secondary progressive MS (PRMS) and progressive relapsing MS by European Medicines Agency and also by Food & Drug Administration (FDA).Mitoxantrone is also used for the treatment of various diseases butalong with these usefulness it has the above serious harmful side effects. The major adverse effect associated with its use iscardio toxicity [34-36]. Although the mechanism of action of mitoxantroneis not fully understood therefore all of the adverse effects of mitoxantrone on immune system need to be explored [37]. The common adverse effects on the immune system includes several immunomodulatory effects, inducing macrophage-mediated suppression of B-cell, T-helper and T-cytotoxic lymphocyte function [38]. Therefore, cardiac monitoring of mitoxantrone patients is done by estimation of left ventricular ejection fraction (LVFE) by the use of echocardiography technique. But by use of this technique we can not detect the early cardiac dysfunction [39-40]. Life time dosage of mitoxantrone is limited due to its potential toxicity and due to its cardiac and hematologic adverse reactions. Approximately in 26.6% of patients having mitoxantrone dosage of 140mg/m^2 body surface area has been reported to have congestive heart failure (CHF) [41,42]. The myocardial damage in which LVFE reduces isoccurring as a result of cardio toxicity of anthracycline family that is considering to be dose-dependent. In rare cases heart dysfunctions such as electrocardiogram (ECG) changes, arrhythmias, CHF and clinical heart failure may occur as a result of cardio toxicity [43]. Data collected on mitoxantrone-related cardio toxicity in MS are less, thus incident rate for symptomatic heart failure ranges between 0.2% and 2.0% [26,35,36,44,45]. According to Paul et al., LVEF reduction was observed in early stage of mitoxantrone treatment approximately in 4 out of 18 prospectively assessed patients [46].

Mitoxantrone loaded with nanoparticles (NP)

Nano particles are nowadays widely used for delivering of various drugs astheyenhance the solubility of drugs,their distributions to the target tissues or cells.NP drug-delivery systems increase the absorption of drugs,increase its bioavailability and protect drug from degradationinside the gastrointestinal tract [47,48]. There a number of studies done using nanoparticles as a drug carrier for mitoxantrone.Super paramagnetic iron oxide nanoparticles(SIPONS) are consider to be safe and favorable [49]. Nowadays most of the of drugs are doped with nanoparticles in order to increase theavailability to cells.The SPIONs are combined with external magnetic field so called Magnetic drug targeting (MDT). The MDT has solve many problems related to chemotherapeutic methods in patients of cancer. This is expected that drug will approach the targeted region in the cancer patients. Studies were done on rabbit in which it was observed that mitoxantrone capped with SPIONS increased the function of drug including strong magnetic field. This approach also decrease the drug toxicity and dosage quantity[50].The study showed that mitoxantrone loaded with SPION and unloaded show same penetrating and killing effect but unloaded do not have better cellular viability [50].Thus loaded mitoxantrone effect more effectively on complex multicellular tissues and its microenvironment as compared to unloaded [51]. The function of MP-SiO_2 NPs depend on its complex with boronic acid ligands. When the anticancer drugs likemitoxantrone are loaded in pores of MP-SiO_2 NPs and capping was done by means by anticancer drug gossypol. The combination of these two-drug-functionalized MP-SiO_2NPs provide a very functional chemotherapeutic treatment. An *in vitro* studies showed that environmental conditions such as acidic conditions unlocked the caps of MP-SiO_2 NPs. Thus, this unlocking of caps cause the hydrolysis of capping unit of boronate ester by acid and ester bridges of boronate are separated by lactate ligand. The gossypol-capped mitoxantrone-loaded have better cytotoxicity towards cancerous cells. The comparative studies showed that the gossypol-capped mitoxantrone-loaded MP-SiO_2NPs show more better death of cancer cells as compared to cyclodextrin-capped mitoxantrone-loaded [52].

Doping of mitoxantrone with methionine increase its cytotoxic effect and reduces its cardiotoxicity as compared to mitoxantrone alone. Methionine doped with mitoxantrone as L- methionine-conjugated mitoxantrone (MX-MET) molecule and generally

refered as WRC-213.The WRC-213 showed the formation of tail in DNA and also reduce cytotoxicity as compared to MX H9c2 cells [53]. Further studies also showed that mitoxantronedoped with 1,4-bis-L-methionine showed less toxicity,better breaking of cancer cells DNA and less drug resistance profile [54].

CONCLUSIONS AND FUTURE PERSPECTIVES

Mitoxantroneis an anticancer drug having wide range of antitumor activity.The starting material used for the synthesis of mitoxantrone isleucotetrahydroxyanthraquinone.It has been synthesized to reduce the cardiac toxicity of anthracycline drugs. By structure elucidation mitoxantrone have different structure analogues on the bases of different substitution at position 1,2,3,4 of its structure.Mitoxantrone is aninhibitor of DNA enzyme topoisomerase-II.The dosage of mitoxantronegiven to patients is limited due to its potential cardiactoxicity and due to its hematologic adverse reactions. The potency and reduction in toxicity can be obtained further through proper research in mammal models by doing modification in the drug and its use of combination with other drugs that neutralize its effect in the heart.

AUTHORS' CONTRIBUTION

SB and TM provided the concept and designed the manuscript. NA, KK, AU and MA participated in the discussion during preparation of the manuscript. All authors read and approved the final manuscript of this review.

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Cite this article

Badshah SL, Malik T, Ahmad N, Khan K, Ullah A, et al. (2017) Mitoxantrones for Cancer Treatment and there Side Effects. J Clin Pharm 3(1): 1011.