

Review Article

Adriamycin's Hepatotoxic Effect Associated With Local Renin Angiotensin System

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Abstract

Cancer patient's number is going to scale up every year. Adriamycin (ADR) is one of the most effective anticancer drug against to solid tumors. Unfortunately, the drug has a undesired side effect on some tissue including heart, liver, kidney, pancreas. Although many studies found that ADR's toxic effect relate to oxidative stress, the exact molecular mechanisms underlying of its side effect has not completely understood. There is limited study researched the relationship between liver exposed to ADR and local renin-angiotensin system (RAS) in the liver. However, the available data suggest that RAS would act as triggers or accelerator for the development of hepatotoxicity induced by ADR. Future studies will be necessary to have outlined the relationship.

Keywords: Adriamycin; Hepatotoxicity; Renin-angiotensin system; Oxidative stress

The tumor has been very high prevalence at worldwide [1]. Some drugs including some anticancer have been well identified to cause to hepatotoxicity [2]. One of well-known is ADR [3].

Adriamycin is an anthracycline antibiotic commonly used in patients suffering from soft tissue cancer, e.g. breast, ovary, lungs [4, 5], and hepatocellular carcinoma [6]. However, it, unfortunately, has some adverse effect on some organ, e.g. heart [7], liver [8], kidney [9]. The ADR's toxicity is related to dose (cumulatively 550 mg/m²) [10] and time manner [11]. A previous study demonstrated to hepatotoxicity induced by ADR by using to enhance aspartate amino transaminase and alanine amino transaminase levels in animals [12]. Some reasons can explain why the ADR's side effect on liver tissue. One of them is that the liver is the ability of detoxification of toxic drugs and chemicals [13]. Moreover, one previous study was indicated that ADR cause to depress the metabolic

activity of liver by inhibiting CYP3A function [14] which role in the liver is drug metabolism [15]. The second of them is that ADR has been shown to accumulate at mitochondria [7, 8]. The liver has high density and content of mitochondria due to its function [16]. Although many studies agreed to ADR's side effect on tissue related to oxidative stress [7,17-19], it could not be completely understood to its exact mechanism to induce a toxic impact on the tissue so far. This mechanism is a crucial question to get solved for a patient with cancer for the elevation of ADR's therapeutic effects. ADR might crosstalk some local factor at tissue to amplify its side impact. That is why the review was written to outline a close relationship between ADR's toxic influence on the liver and the renin-angiotensin system (RAS) in the liver. There are limited studies to explore the interaction between ADR's undesired impact on liver and local or tissue RAS in the liver.

RAS is important endocrine cascade to regulate the salt-water balance [20]. RAS also modulate to body metabolic process [21]. The most efficient agent of RAS is angiotensin-II who has systemic and local effects including paracrine and autocrine [22]. Many tissues has itself local RAS activity [23], such as liver [24].

Angiotensin-II has been indicated to have some pathophysiologic roles, e.g. inflammation, oxidant and prothrombic effect [21]. RAS activation reported in the patients with liver cirrhosis [25,26], liver inflammation, nonalcoholic fatty liver disease [27], fibrosis [24,28] and related to elevation of portal vein pressure as well. RAS triggers oxidative stress at liver [29]. RAS may, therefore, closely associate with chronic liver disease. Efe et al. reported having a positive correlation between plasma ACE level and patient with liver fibrosis [30]. Portal hypertension is interacted with RAS and the sympathetic system, resulting in retention of water and salt then ascites [31]. Furthermore, angiotensin-II type-1 receptor (AT-1) at liver plays a role in hepatic stellate cell activation by phosphorylation of Janus kinase-2 [32]. Besides, hepatic fibrosis was reported to attenuate at AT-1 knockdown mice. Also, Ang-II stimulates the hepatic stellate cell for production more Ang-II [29].

The RAS activation is not only important to the liver, but also some kidney disease. For example, a recent study was suggested that the source of podocyte injury induced by renal angiotensin-II originated from the liver [33, 34]. It has well known that the liver is a source of blood angiotensinogen in normal physiology condition [21].

There is still no effective pharmacologic treatment for ADR's adverse effect on the liver tissue so far. Recent data from animal [35-37] and human [38,39] studies suggest that the counteraction of RAS would be of importance in reducing side effects of ADR. So, the aim of the present review was to analyze the participation of RAS on hepatotoxicity induced by Adriamycin.

It suggested that inhibition of hepatic RAS had a beneficial effect to suppress steatosis and fibrosis [27]. The local RAS has become so important to under pathophysiologic condition at liver because of low express of RAS component [27]. Hence, elevation of Ang-II is closely fields of fibrosis [29]. There is only a few study researching the relationship between hepatotoxicity induced by adriamycin and local RAS in the liver tissue. One of them reported that adriamycin initiates to sympathetic activity, renin-angiotensin system activity including plasma renin and angiotensin increasing without elevation of vasopressin [40]. The other found that its side effect on the liver associated with oxidative stress and angiotensin converting enzyme blockers reduced to oxidative stress-induced ADR [41]. A undesired side effect of ADR at the liver is reported to relate to mitochondrial dysfunction relying on depolarization of mitochondrial membrane potential and production of ATP [8].

The drug does not just affect one tissue. In a study, adriamycin infusion was used as a model of congestive heart failure. They found the decrease heart function, increase blood pressure by early activation of RAS and later activation

of sympathetic system activation and hepatic congestion as well [42]. Angiogenesis participate to metastasis of carcinomas. Also, the other important knowledge about RAS to be known plays a crucial role to regulate the angiogenesis [25]. So, RAS antagonists would be useful in attenuating ADR induced hepatotoxicity as well as metastasis of cancer by inhibition of angiogenesis. AT1 receptor antagonist has been reported to diminish to liver cirrhosis by suppression vascular endothelial growth factor [25].

Literature has availed limited studies on the interaction between ADR's side effect on the liver and local RAS so far. However, there are some clues the relationship. Because both ADR and Ang-II play important roles in oxidative stress-related with some liver pathologies, ADR may crosstalk with local Ang-II production in the liver. The local Ang-II would act an accelerator of its undesired side effect. To get better understood, it will need to explore the relationship in future.

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