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Review article

Combretastatins: *In vitro* structure-activity relationship, mode of action and current clinical status

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ABSTRACT

For the first time combretastatins were isolated from African willow tree *Combretum Caffrum*. Subsequent studies have shown the impact of combretastatin A4 phosphate, a water-soluble prodrug, on endothelial cells in tumor vascular system. The same effect was not observed in the vascular system. This selectivity is associated with combretastatins mechanism of action: binding to colchicine domain of microtubules, which affects the cytoskeleton functionality of immature endothelial cells. At the same time, combretastatins directly induce cell death via apoptosis and/or mitotic catastrophe pathways. The combination of both elements makes combretastatin an anticancer compound of high efficiency.

The *cis*-configuration is crucial for its biological activity. To date, many derivatives were synthesized. The attempts to resolve spontaneous isomerization to less active *trans*-stilbene derivative are still in progress. This issue seems to be overcome by incorporation of the ethene bridge with heterocyclic moiety in combretastatins structure. This modification retains the *cis*-configuration and prevents isomerization. Nevertheless, combretastatin A4 phosphate disodium is still the most potent compound of this group.

The combination therapy, which is the most effective treatment, includes combretastatin A4 phosphate (CA4P) and conventional chemotherapeutics and/or radiotherapy. CA4P is relatively well tolerated giving adverse events of moderate severity, which includes: nausea, vomiting, headache, and tumor pain. The aforementioned effects subside on the day of drug administration or on the following day.

Contents

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Introduction

The basic method of treatment of neoplastic changes having a solid tumor characteristic is radical surgery, which can be preceded by chemotherapy and/or radiotherapy aimed at reducing the tumor (i.e. neoadjuvant therapy) [1]. When surgical removal of the tumor is not possible to conduct, only chemotherapy or radiotherapy or their combination is used.

Still used, standard cancer therapy is based on an application of natural and synthetic cytostatic drugs and hormone therapy.

Conventional treatment results in system-wide side effects because commonly used drugs are not selective and are cytotoxic for both – cancer and healthy cells – especially for rapidly dividing cells such as bone marrow, epithelial and lymphatic cells [2].

Modern anticancer therapeutic strategies are based on inhibition of angiogenesis within the tumor tissue. Vascular disrupting agents (VDAs) can rapidly and selectively inhibit angiogenesis in the tumor causing tumor cell death due to ischemia [3]. One of the compounds from the VDAs group is combretastatin A4 (CA-4, Fig. 1A). It shows properties of inhibiting tubulin depolarization in endothelium cells of tumor blood vessels [4]. Simultaneously, CA-4 can directly cause cancer cells death by inducing apoptosis and/or mitotic catastrophe [5]. Due to its antiangiogenic activity, CA-4 is used in thyroid cancer treatment.

History of combretastatins and their derivatives

The first-known compound of combretastatin with potent antitubulin activity was a derivative labeled A1, which was isolated in the late 80 s from the bark of African willow *Combretum Caffrum* [6]. In subsequent years, attempts were made to discover and characterized novel compounds with *cis*-stilbene core, which would exhibit an improved cytotoxic action by inhibiting the polymerization of microtubules. As a result of these studies combretastatin A4 (CA-4) was described and became a leading structure that efficiently induce cell death and powerfully inhibit *in vitro* tubulin polymerization. Unfortunately, due to poor solubility in aqueous solutions, it was ineffective in clinical trials. Therefore, a method of assessing combretastatin A4 phosphate (CA4P), which is a water-soluble CA-4 prodrug, was developed [7]. In living organisms it is converted to the active form of combretastatin A4, due to the presence of non-specific phosphatases [8]. The next stages in the history of obtaining combretastatin were attempts to get the structures with improved chemical stability by reduce ability of spontaneous *cis-trans* isomerization. This is essential because the *cis*-stilbene isomers are many times more biologically active than the *trans*-stilbene analogs, which can bind to tubulin, but are unable to inhibit microtubule assembly [9]. In order to block this process, heterocyclic moieties are placed into the ethene bridge or between the ethene bridge and one of the phenyl rings. Numerous combretastatin derivatives modified on the double bond with different heterocyclic rings such as isoxazole, indole, β-lactam, *trans*-methylpyrazoline, pyrazole, pyrazoline, cyclohexenone, oxadiazoline were synthesized and their *in vitro* cytotoxic properties were tested [10–17].

Combretastatin mechanism of action

Compounds affecting the functioning of microtubules can be divided according to its mechanism of action into two main groups: stabilizing and destabilizing the microtubules. Both groups disturb the dynamic balance between the shortening and lengthening of microtubules. Inhibition of microtubule polymerization is specific for destabilizing compounds, which have an affinity to colchicine or *Vinca* alkaloids domain. Compounds' stabilizing the microtubule structure prevents their depolymerization, which

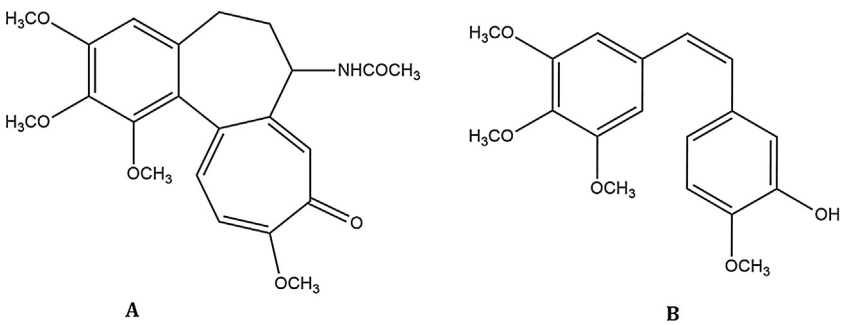

Fig. 1. Chemical structure of colchicine (A) and combretastatin A4 (B).