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Review

Cancer combination therapies with artemisinin-type drugs

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ABSTRACT

Artemisia annua L. is a Chinese medicinal plant, which is used throughout Asia and Africa as tea or press juice to treat malaria. The bioactivity of its chemical constituent, artemisinin is, however, much broader. We and others found that artemisinin and its derivatives also exert profound activity against tumor cells *in vitro* and *in vivo*. Should artemisinin-type drugs be applied routinely in clinical oncology in the future, then it should probably be as part of combination therapy regimens rather than as monotherapy. In the present review, I give a comprehensive overview on synergistic and additive effects of artemisinin-type drugs in combination with different types of cytotoxic agents and treatment modalities: (a) standard chemotherapeutic drugs, (b) radiotherapy and photodynamic therapy, (c) established drugs for other indications than cancer, (d) novel synthetic compounds, (e) natural products and natural product derivatives, (f) therapeutic antibodies and recombinant proteins, and (g) RNA interference. I also summarize the activity of artemisinin-type drugs towards multidrug-resistant cells and tumor cells with other drug resistance phenomena. As synergistic interactions may not only occur in tumor cells, toxic reactions in normal cells (hepatotoxicity, drug interactions) were also considered. This review summarizes the scientific literature of more than 20 years until the end of 2016.

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Abbreviations: ACE, angiotensin I-converting enzyme; ACT, artemisinin-based combination therapy; Akt, AKT serine/threonine kinase, *v-akt* murine thymoma viral oncogene homologue; AMP, adenosine monophosphate; ARE, arteether; ARM, artemether; ARS, artemisinin; ART, artesunate; BCL-XL, break point cluster X, long; BCRP, breast cancer resistance protein; BMI1, B-lymphoma Mo-MLV insertion region 1 homologue (mouse); Ca, carcinoma; CDK2, cyclin-dependent kinase 2; CIP, cyclin-interacting protein; CRISPR, clustered regulatory interspaced short palindromic repeats; CYP, cytochrome P450 monooxygenase; DHA, dihydroartemisinin; DR5, death receptor 5; ERK1/2, extracellular signal-regulated kinase 1/2; FAS, Fas cell surface death receptor; FDA, Food and Drug Administration; Fos, FBJ murine osteosarcoma viral (*v-fos*) oncogene homologue; G6PD, glucose-6-phosphate dehydrogenase; GSH, reduced glutathione; GSSG, oxidized glutathione; GST, glutathione S-transferase; HDAC, histone deacetylase; HIF-1α, hypoxia-induced factor 1-alpha; HSP, heat shock protein; KIP, kinase-interacting protein; MAPK, mitogen-activated protein kinase; MDR, multidrug resistance; MMP, matrix metalloproteinase; MRP, multidrug resistance-related protein; $NADP^+$, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa-B; NHL, non-Hodgkin lymphoma; PARK7, Parkinsonism-associated deglycase 7; P-gp, P-glycoprotein; PUVA, psoralen plus UVA light therapy; RAC-1, Ras-related C3 Botulinum toxin substrate 1 (Rho family); RAD51, RAD51 (radiation 51) recombinase; R-CHOP, rituximab, cyclophosphamide, vincristine, prednisone combination therapy; ROS, reactive oxygen species; Sp1, specificity protein 1 transcription factor; TCM, traditional Chinese medicine; TRAIL, tumor necrose factor receptor apoptosis-inducing ligand; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; XIAP, X-linked inhibitor of apoptosis; YY1, yin yang 1 transcription factor.

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1. Introduction

Artemisinin (ARS) from the Sweet wormwood (*qinhao*, *Artemisia annua* L., Asteraceae) is a medicinal plant used in Chinese medicine to treat chills and fever. In the 1970 and 1980s it turned out that the drug reveals surprisingly strong efficacy towards *Plasmodia*. Nowadays, artemisinin belongs to the standard treatment protocols to treat malaria. Because artemisinin saved millions of lives of malaria patients, Youyou Tu, who first identified the malaria activity of *A. annua*, was honored with the Nobel Prize for Medicine or Physiology 2015 [1]. Interestingly, *A. annua* preparations (decoctions, tea, press juice) are frequently used outside the official medical system in Asia and Africa to treat malaria [2,3]. During the past years, experimental evidence was accumulated that ARS activity is not restricted to malaria and that it may also be of therapeutic interest for several other diseases, including cancer [4–12]. Should ARS-type drugs ever be used routinely in clinical oncology, then it should be with high probability as part of combination therapy protocols rather than as monotherapy [13–15].

The principles, which are common sense for combination therapy protocols with established anticancer drugs, also have to be applied for combinations with ARS-type drugs, *i.e.* (1) prevention of resistance development by combining drugs with different targets and modes of action; (2) dispersion of side effects to different tissues in the body to minimize the occurrence of severe or fatal toxicities; (3) each constituent of the combination protocol has to reveal anticancer activity, if applied as single drug etc. [16–18]. In the preclinical setting, synergy has to be proven by appropriate biostatistical methods [19,20] in well suitable experimental biological models *in vitro* and *in vivo* [21–25]. Frequently, authors publish their data by claiming synergistic interactions of compound combinations without reliable proof, whether or not the observed effects are indeed synergistic in nature. This is a considerable limitation of many data available in the literature in pharmacology in general and also in the case of ARS-type drugs.

A wealth of results has been published in the literature on additive or synergistic combinations of ARS-type drugs with other compounds to improve tumor growth inhibition in cell lines and in animal experiments (Fig. 1). The intention of the present review was to give an overview of the published data and to outline perspectives for further research developing the most suitable combination therapy protocols for ARS-based cancer therapy.

A central question in this context is about the molecular targets of ARS-type drugs in cancer cells. Despite a plethora of published data, this question is not ultimately resolved. Most likely, this class of compounds acts in a multi-specific manner exhibiting several modes of action at the same time. This is a typical feature of most – if not all – natural products [26]. The endoperoxide moiety of ARS-type drugs can be opened leading to the formation of radical oxygen species and carbon-centered radical molecules. This process is facilitated by free ferrous iron or iron-bound proteins (*e.g.* heme) in a Fenton-type reaction. These radical molecules may exert a broad range of detrimental effects in cancer cells. As previously outlined, the activity of antitumor drugs in general may be categorized as (1) mechanisms acting upstream of the actual drug target, (2) target site mechanisms, and (3) mechanisms acting downstream of the drug targets [27]. This model may also be applied for ARS-type drugs. As described in great detail in a recent review [28], molecular modes of action of ARS-type drugs in cancer cells include:

(1) Upstream mechanisms: antioxidant response mechanisms, receptor signaling pathways (*e.g.* EGFR, WNT/β-catenin, BCR/ABL)
(2) Target site mechanisms: DNA damage and repair mechanisms, alkylation of target proteins (*e.g.* TCTP, LDH etc.), cell cycle arrest, neoangiogenesis, invasion and metastasis
(3) Downstream mechanisms: apoptotic and non-apoptotic cell death (autophagy, ferroptosis).

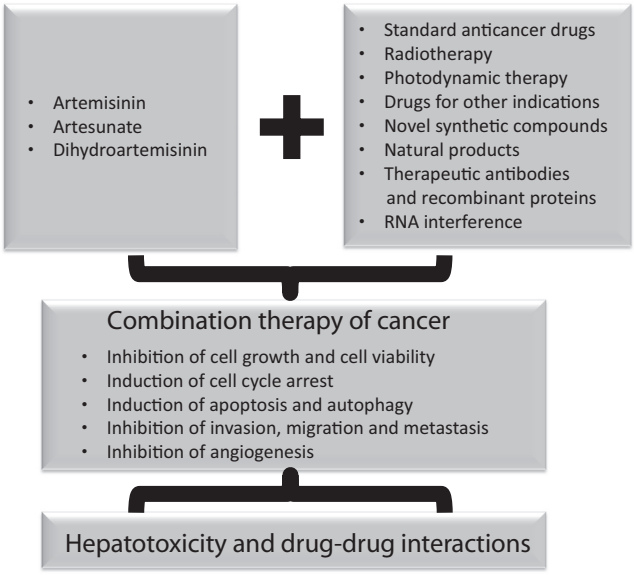

Fig. 1. Synopsis of mechanisms involved in combination treatments between ARS-based drugs and other treatment modalities for cancer therapy.

2. Combination with standard chemotherapy

In the past few years, a plethora of papers appeared on the interaction of ARS-type drugs with clinically established anticancer agents, many of which are acting directly or indirectly on tumor DNA by damaging its integrity in one or another way (the DNA topoisomerase II inhibitor doxorubicin, the adduct-forming platin compounds, the alkylating agents temozolomide) or disturbing DNA-biosynthesis (gemcitabine, cytarabine) (Table 1). Since ARS-type drugs cause oxidative DNA lesions and double strand breaks [29–35], it is worth hypothesizing that their interaction with DNA-affecting anticancer drugs may provoke enhanced tumor cell killing. Indeed, additive to synergistic interactions of ARS, DHA, or ART have been observed in combination with standard anticancer drugs towards tumor cell lines of diverse origin, *e.g.* hematopoetic tumors (leukemia, multiple myeloma) as well as epithelial carcinoma (of breast, ovarian, lung, brain tumor, liver, prostate, or pancreas). Importantly, these effects were not only measured *in vitro* but also *in vivo*, which raises the potential clinical utility of this kind of drug combinations.

In case that ARS-type drugs should ever reach clinical routine application for cancer therapy, it is important to investigate the