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COMMENTARY

Back to the future of oridonin: again, compound from medicinal herb shows potent antileukemia efficacies *in vitro* and *in vivo*

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Traditional Chinese Medicine (TCM) has been widely and successfully used in treating illnesses ranging from inflammation to cancer, and compounds from medicinal herbs and minerals are playing more and more important roles in taming various kinds of diseases [1], exemplified by artemisinin and arsenic trioxide (ATO). Artemisinin (or Qinghaosu in Chinese) is isolated from a plant called sweet wormwood (*Artemisia annua*; or Qinghao in Chinese) which has been used as an antipyretic remedy for more than 1500 years in China. Artemisinin has impressive parasiticidal properties *in vitro* and *in vivo*, and is now one of the most important class of antimalarial agents [2, 3]. ATO is a common, naturally occurring substance which had been used in China for a long time as a therapeutic agent for some severe diseases with the ancient philosophy of 'treating an evil with a toxic' [4]. In 1990s, ATO was shown to be able to cause partial differentiation at low dose and apoptosis at high concentration of acute promyelocytic leukemia (APL) cells [5], and induce complete remission in 90% of patients with relapsed or refractory APL [6-8]. These paradigms suggest that TCM is the treasure house not only for the Chinese people, but also for the whole human beings. It is our responsibility to develop evidence-based therapeutic approaches from TCM for diseases with poor prognosis.

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Isodon plant *Rabdosia rubescens* which is called Donglingcao in China, is a Chinese medicinal herb used widely in provinces including Henan. The aerial parts of RR and other species of the same genus has been reported to have the functions of clearing "heat" and "toxicity", nourishing "yin", removing "blood stasis", and relieving swelling. RR has been used to treat stomach ache, sore throat and cough. Moreover, RR and its extracts have been shown to be able to suppress disease progress, reduce tumor burden, alleviate syndrome and prolong survival in patients with gastric carcinoma, esophageal, liver and prostate cancers [1]. Interestingly, other Isodon plants including *Isodon japonicus* Hara (IJ) and *I. trichocarpus* (IT) are also applied as home remedies for similar disorders in Japan and Korea. These reports suggest that Isodon plants should have at least one essential antitumor component. In 1970s, a bitter tetracycline diterpenoid compound, oridonin, was isolated from RR, IJ, and IT separately, and was shown to be a potent apoptosis inducer in a variety of cancer cells [9-12]. However, whether oridonin can be used in the selected setting of hematology/oncology, and which types of hematologic malignancies could represent the most sensitive ones to oridonin treatment, remain obscure.

The success of using ATO and *all-trans* retinoic acid (ATRA) in taming APL has been the impetus for us to develop therapeutic approaches for other subtypes of leukemia with poor prognosis. Both ATO and ATRA target the PML-RARα, a fusion protein resulted from t(15;17) chromosomal translocation which plays a critical role in

APL leukemogenesis [13-15], suggesting that oncoproteins crucial for leukemia pathogenesis could be ideal therapeutic targets. M2 type acute myeloid leukemia (AML-M2) accounts for 25% of all AML cases, and is characterized by the presence of t(8;21) chromosomal translocation; and the resultant AML1-ETO (AE) fusion protein is detected in 40% to 80% of AML-M2 patients. AE oncoprotein plays a critical role in t(8;21) leukemia pathogenesis. Though reports showed that t(8;21) was a favorable prognostic factor for AML [16], patients with t(8;21) AML in China and some other countries had a median survival time of less than two years [17]. For these reasons, AML-M2 with t(8;21) has been a research focus in our institute since 2000, aiming at elucidating leukemogenesis and developing therapeutic approaches.

We investigated the effects of oridonin on a spectrum of leukemic cells including the t(8;21)-harboring Kasumi-1 cell line and primary leukemia cells isolated from patients with *de novo* or relapsed/refractory t(8;21) AML. In our work, cell proliferation, cell viability, cell cycle, mitochondrial transmembrane potential, externalization of phosphatidylserine, and *in situ* cell death were carefully analyzed. We found that among cells tested, t(8;21)-harboring cells were the most sensitive ones to oridonin treatment [18]. Oridonin at clinical available concentrations inhibited growth and induced programmed cell death of t(8;21) leukemic cells through insult of mitochondria functions and unleash of apoptosis machineries, down-regulation of apoptosis antagonist Bcl-2, and activation of apoptosis executioners including caspase-9 and -3. Since AE fusion protein is critical to leukemogenesis, we assessed the impact of oridonin on AE and found that oridonin treatment could cause a caspase-3 dependent degradation of AE, and the aspartic acid residue at position 188 of AE (D188) was identified as the cleavage site. The catabolism of AE could lead to reprogramming of its target genes. Intriguingly, in murine models of t(8;21) AML, oridonin induced apoptosis of leukemic cells and significantly prolonged life span of mice bearing t(8;21) leukemic cells, and inhibited tumor growth in nude mice. These antitumor effects seemed to be superior to that of cytosine arabinoside (Ara-C), because oridonin at 7.5 to 15 mg/kg per day exerted a more profound antileukemia efficacy than low dose Ara-C, and did not cause suppression of bone marrow or loss of body weight as compared with mice treated with high dose Ara-C. A synergic effect was seen in mice treated with low dose Ara-C and oridonin. These data suggest that oridonin could be effective in treating human t(8;21) leukemia, and potential clinical trial should be performed to evaluate oridonin as a drug against t(8;21) AML [18].

More than three decades have passed since the isolation of oridonin from the Chinese medicinal herb RR, but whether oridonin could find clinical application, and which kind of cancer could be the most sensitive one to oridonin treatment, warrant further investigation. Our results clearly demonstrate the potent antileukemia efficacies of oridonin on t(8;21) AML with low adverse effect, opening a potential bright future for oridonin treatment which might provide benefits for patients with t(8;21) AML.

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