Cytotoxic Effect of Artemisinin and Its Derivatives on Human Osteosarcoma Cell Lines

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Background: *Osteosarcoma is the most common, non-hematopoietic, primary bone cancer. Current standard treatment is to use neoadjuvant chemotherapy followed by surgical resection. However, many complications from chemotherapy have been reported. Some studies have reported artemisinin derivatives showed cytotoxic and anti-angiogenic properties.*
Objective: *To investigate cytotoxic properties of artemisinin and its derivatives on human osteosarcoma cell lines.*
Material and Method: *Osteosarcoma cell lines (MG63 and 148B) were continuously cultured. MTT assay was used to evaluate cytotoxic properties of artemisinin derivatives at 48 hours of incubation. These cell lines were also tested against doxorubicin as a control. Each IC50 value represented the mean of at least 3 experiments. Independent t-test was used to test differences between groups.*
Results: *Artemisinin and its derivatives at micromolar range exhibited anti-cancer growth activities in human osteosarcoma cell lines. Among them, RKA182 the new synthetic tetraoxane is the most effective in inhibiting cell growth. In addition, water-soluble properties of drugs may be the main factor in cytotoxicity.*
Conclusion: *The promising result shows that artemisinin and its derivative inhibits the growth of human osteosarcoma cells. This study indicated that RKA182 may be a potent and promising agent to combat osteosarcoma. Further studies should be conducted of new synthetic drugs as possible anti-cancer drugs or adjuvant therapy in the clinical treatment of osteosarcoma.*

Keywords: *Artemisinin derivatives, MTT, Human osteosarcoma cells*

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Osteosarcoma is one of the most common, non-hematopoietic, primary malignant bone tumors and occurs mainly in children and young adults. The primary treatment is a multidisciplinary approach including surgery and neoadjuvant chemotherapy. In localized osteosarcoma patients, the five-year survival rates are approximately 70%[1]. However, the prognosis for patients is quite poor[2] because of a high potential to invade and metastasize. Moreover, the drug resistance and extensive side effects of the chemotherapy drugs remain serious problems that reduce the quality of life for the patients. Although neoadjuvant chemotherapy can be effective, multi-drug resistant cases are common, especially with doxorubicin and cisplatin[3]. Over the past decade, no significant improvement has been made in chemotherapy for osteosarcoma[4]. Hence, an urgent need exists for safer and more effective chemotherapy agents.

Artemisinin is a drug extracted from the wormwood *Artemisia annua*. Its derivatives including artesunate, artemether and dihydroartemisinin have been approved by the Food and Drug administration for the treatment of malaria[5-7]. During its many years of use, artemisinin derivatives have been well tolerated by patients, with little toxicity and no obvious side effects[8,9]. Recently, a new range of synthetic tetraoxanes was selected for preclinical development as an anti-malarial agent. Moreover, they showed no side effects/toxicity by preliminary in vitro and in vivo studies[10]. Among them, RKA182 is a synthetic tetraoxane with outstanding in vitro and in vivo antimalarial activities[11,12].

Recently, it has been reported that artemisinin derivatives also exert potent antitumor activity towards

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a variety of human cancer cells in culture[13-18], as well as in certain animal models[19]. The mechanism for an anti-cancer activity of artemisinin derivatives is induction of tumor cell apoptosis or oncosis[17,20]. Apoptosis is a form of programmed cell death which occurs through activation of cell-intrinsic suicide machinery. It is a hallmark of anti-cancer drug-induced cell death. Apoptosis is considered the major form of cell death in various physiological events.

Artemisinin is sesquiterpene lactone peroxide containing an endoperoxide moiety[44], which forms free radicals when it reacts with iron. Iron is necessary for cell division and proliferation. Compared with normal cells, cancer cells have a tumor aggressiveness-dependent higher number of cell surface transferrin receptors[21] that pick up iron via interaction with the plasma iron-carrying protein transfer. Therefore, cancer cells would be selectively more susceptible to the cytotoxicity of artemisinin because of their higher rates of iron uptake.

Other possible mechanisms for the anti-cancer activity of artemisinin derivatives include inhibiting angiogenesis and down regulation of vascular endothelial growth factor expression, inducing DNA damage, suppressing the hyperactive Wnt/β-catenin pathway[22] and inhibiting tumor invasion and metastasis[23]. Apart from these, the oxidative stress seems to be necessary for the anti-malarial effects of artemisinin derivatives[8,9] and play an important role in anti-cancer activity[24]. Little is known about the effects of artemisinin derivatives on human osteosarcoma cells. An in vitro and in vivo present study concluded that artesunate, which is an artemisinin derivative, is a promising candidate for the treatment of osteosarcoma[25]. The authors evaluated the cytotoxicity activity of artemisinin derivatives and new synthetic tetraoxane (RKA182) in human osteosarcoma cell lines in vitro. The authors also investigated the possible factor mediating the anti-cancer effect of these drugs in these cell lines.

Material and Method

The present study was approved by our institutional research ethics board before starting.

Cell culture

Human osteosarcoma cell lines MG63 and 148B were both obtained from the School of Medicine Kanazawa University, Japan. Human osteosarcoma cell lines were cultivated in Dulbecco's Minimum Essential Medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum (Gibco BRL, Grand Island, NY), 100 U/ml gentamycin. Cultures were maintained at 37°C in a 5% (v/v) CO_2 humidified atmosphere. The medium was changed every three days and cells were passaged twice a week.

Chemicals and reagents

Solutions of artemisinin and its derivatives (Guilin Pharmaceutical Co. Ltd, Guangxi, China) were prepared in DMSO and diluted in cell culture media to the indicated final concentrations. Doxorubicin was obtained from Pharmaland (1982) Co. Ltd, Bangkok, Thailand. RKA182 was obtained from Professor PM O'Neill, Department of Chemistry, The University of Liverpool and Professor SA Ward, The Liverpool School of Tropical Medicine, Liverpool, UK. 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) were produced from Invitrogen™.

Cytotoxicity assay (MTT assay)

The authors used MTT assay to evaluate how cell viability and proliferation forms the basis for numerous in vitro assays of a cell population's response to external factors such as temp, pH etc. Yellow tetrazolium MTT (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide) was reduced by metabolically viable cells, in part by the action of mitochondrial reductase enzyme and media then changed to purple caused by intracellular formazan. Conversely, when metabolic events lead to apoptosis, the number of assay steps can be minimized. The resulting purple solution was spectropho to metrically measured. To evaluate whether the inhibitory effect of artemisinin derivatives on cell growth is general or selective, the authors used both MG63 and 148B cell lines as a control.

MG63 and 148B human osteosarcoma cells were diluted at a density of 5,000 cells/well and were seeded in 96-well plates. After overnight incubation, the media were replaced with fresh media containing six groups of drugs consist of doxorubicin as a standard control at 0.1, 0.5, 1, 5, 10, 50 and 100 μM respectively, artemisinin and artemether at 10, 25, 75, 100, 200 and 500 μM, respectively, artesunate, dihydroartemisinin and RKA182 at 1, 5, 10, 25, 50, 100 and 200 μM, respectively. Then, the cells were cultured for 48 hours. Control wells received no drug. On the second day of culture, 10 μl of MTT (5 mg/ml) solution was added to each well. After that, the plates were incubated at 37°C for another four hours until purple precipitate was visible. The media were then discarded and 100 μl of

detergent reagent, dimethyl sulfoxide (DMSO; Sigma) was added to dissolve the formazan crystals, and left at room temperature in the dark for two hours. Finally, absorbance at 600 nm (OD_{600}) was recorded with a spectrophotometer (Anthos 2010; Dynatech Laboratories, Inc., Chantilly, VA, USA). The rate of growth inhibition was calculated as: IR = (1-$OD_{600,test}$/$OD_{600,con}$) x 100%, where IR is inhibition rate, $OD_{600,test}$ is OD_{600} of test well and $OD_{600,con}$ is OD_{600} of control well.

Assessment of cell morphology

After the drugs exposure, cell morphology was examined by phase-contrast light microscopy (Olympus, Tokyo, Japan). To confirm morphological changes of the cells, human osteosarcoma cells, treated with or without the drugs in each group for 48 hours, were collected and fixed with 4% formaldehyde for 30 minutes. After, they were washed three times with phosphate buffer saline solution (PBS), stained with 10 µg/ml Hoechst 33342; then, examined the morphological changes under microscope (OEM BM-501T, China).

Electron microscopy

Human osteosarcoma cells were fixed with 2.5% (v/v) glutaraldehyde in 0.1 mol/L PBS (pH 7.4) for 2 hours. After, they were washed with PBS and post-fixed in 0.01 g/ml osmium tetroxide for 1 hour. Human osteosarcoma cells were dehydrated in acetone and they embedded in epoxy resin. Ultrathin sections were stained with uranyl acetate and lead citrate. Then, examined the morphological features under a transmission electron microscope (Hitachi S-5000 ultra-high resolution scanning, Japan).

Statistical analysis

The present study was an in vitro experimental study. Because all environments were controlled, all quantitative assays were performed five times. Statistical analysis was performed to analyze the association of the difference between high IC50 and low IC50 groups (IC50 is the median concentration that causes 50% inhibition), performed by Student's t-test. Statistical significance was accepted for *p*-value of <0.05. The data were analyzed with STATA/MP12.

Results

The authors examined the cytotoxic effect of both types of human osteosarcoma cell lines. MTT assays were used to determine the anti-cancer effects of doxorubicin (standard control), artemisinin derivatives and RKA182 on human osteosarcoma cell lines. They were analyzed by using IC50. The data suggested that artemisinin derivatives and RKA182 treatment at 48 hour significantly inhibit the growth of either cell line. It is notable that among them, RKA182 was the most effective and potent in inhibiting osteosarcoma cell growth and different cytotoxic activity was found between these drugs (Fig. 1, 2). Electron microscopic (Fig. 3) were used to evaluate apoptosis in artemisinin after exposure to the drugs at 48 h. They confirmed the cytotoxic activity and apoptosis in both cell lines.

Moreover, the authors found that two groups mainly distinguished the IC50: the high IC50 (IC50 >100 µM) and the low IC50 (IC50 <100 µM) group. Thus, the authors performed testing artemisinin and artemether concentrations between 10-500 µM as a high IC50 group and the low IC_{50} group consists of artesunate, dihydroartemisinin and RKA182 testing concentrations between 1-200 µM. The analyzed data show that the IC50 were significantly different between

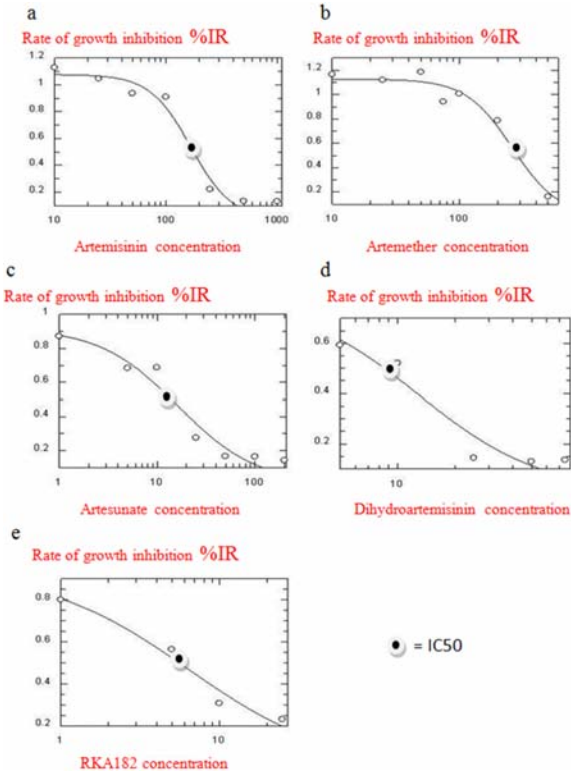

Fig. 1 Mean Inhibitory Concentration (IC50) of MG63 Human Osteosarcoma Cells. (a) IC50 of Artemisinin. (b) IC50 of Artemether. (c) IC50 of Artesunate. (d) IC50 of Dihydroartemisinin. (e) IC50 of RKA182.

groups in both cell lines (MG63; *p*-value = 0.036&148B; *p*-value = 0.028) (Table 1). Although these agents were artemisinin derivatives, they were different in water soluble properties. Artemisinin and Artemether are high IC50 group. There is hydrophobic property. On the other hand, Artesunate, DHA and RKA182 are low IC50 group. There is hydrophilic property. The data show that the IC50 has a statistically significant difference between the two groups.

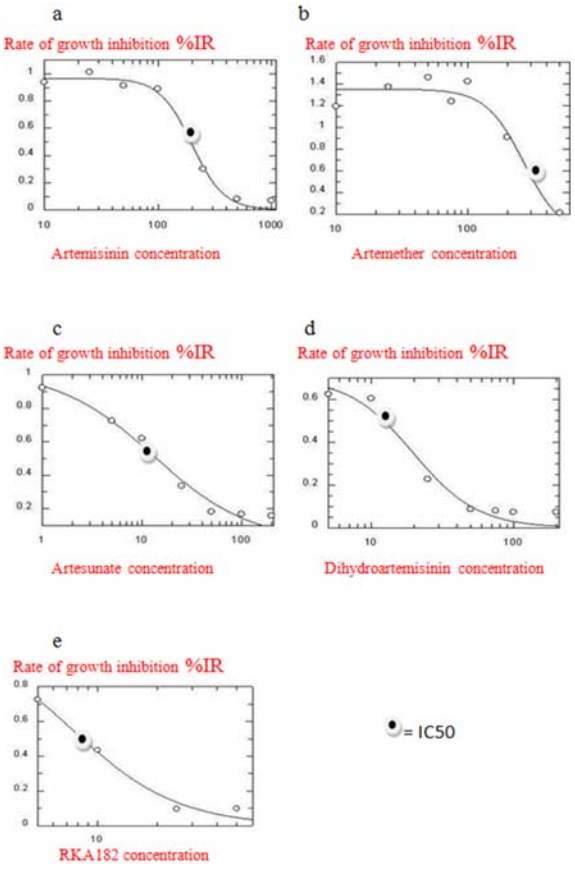

Fig. 2 Mean Inhibitory Concentration (IC50) of 148B Human Osteosarcoma Cells. (a) IC50 of Artemisinin. (b) IC50 of Artemether. (c) IC50 of Artesunate. (d) IC50 of Dihydroartemisinin. (e) IC50 of RKA182.

Discussion

Osteosarcoma is an aggressive malignant bone disorder exerting a high potential to invade and metastasize. Despite the advances neoadjuvant chemotherapy made in improving survival, drug resistance and extensive side effects remain serious problems that reduce the quality of life as well as reduce the prognosis. To improve the prognosis and reduce the side effects in chemotherapy for osteosarcoma, there is an urgent need to develop new anti-cancer agents, which are selected for cytotoxicity with no obvious side effects. Artemisinin and its derivatives have been proved for malarial treatment and have an excellent safety profile. Recently, artesunate was reported to exert potent cytotoxic effects on human osteosarcoma cell line[25]. In this work, we investigated and compared cytotoxicity activities of artemisinin and its derivatives consisting of artemisinin, artesunate,

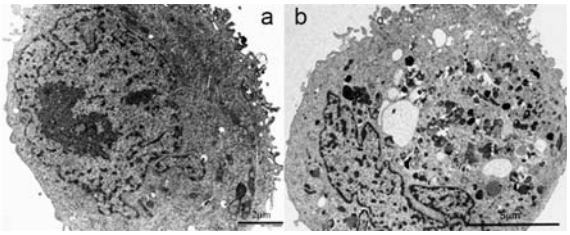

Fig. 3 Effect of Artemisinin on Cell Morphological Change. (a) Osteosarcoma cell was examined for ultrastructural morphological features. (b) After treatment with 80 µM/L dihydroartemisinin for 48 hours. The cell morphological change became to be apoptosis.

Table 1. Mean Inhibitory Concentration (IC50) of MG63 and 148B Human Osteosarcoma Cells

Drug	Mean IC50 of MG63 (µM)	Standard deviation	*p*-value	Mean IC50 of 148B (µM)	Standard deviation	*p*-value
High IC50 group						
Artemisinin	166.6232	±16.84883		178.2879	±16.84883	
Artemether	260.9983	±13.25626	0.036	266.6543	±13.25626	0.028
Low IC50 group						
Artesunate	16.4232	±3.81316		13.1395	±3.81316	
Dihydroartemisinin	12.7932	±3.71787		17.6898	±3.71787	
RKA 182	6.3617	±1.85064		7.4566	±1.85064	

artemether and dihydroartemisinin. Not only were artemisinin derivatives studied, but the authors also investigated and compared the anti-cancer activity of RKA182 that is a new synthetic tetraoxane. However, the molecular mechanism underlying cytotoxicity has not been completely elucidated. Most authors suggested the oxidative stress seems to play an important role in anti-cancer activity. According to our results, artemisinin derivatives and RKA182 at micromolar range exhibited anti-cancer growth activities in human osteosarcoma cell lines. Among them, RKA 182, the new synthetic tetraoxane, was the most effective in inhibiting osteosarcoma cell growth. Additionally, cytotoxic effects of these drugs were separated into high and low IC50. Our findings suggested that the water-soluble property was the main factor in cytotoxicity, i.e. hydrophilic property rather than hydrophobic property.

Although RKA182 is just a representation of a new synthetic tetraoxane group, many drugs have been produced in this group. Further studies of new synthetic drugs as a possible anti-cancer drug or adjuvant therapy in clinical treatment should be conducted to improve the prognosis and reduce the side effects in chemotherapy in osteosarcoma treatment.

Conclusion

The cytotoxicity effects of artemisinin derivatives and RKA182 on human osteosarcoma cells were investigated. These drugs can inhibit the growth of osteosarcoma cell lines and the intrinsic apoptosis pathway may be involved in the process. These results suggest that the new synthetic tetraoxane is expected to be adapted to a new osteosarcoma treatment. This report provides first evidence that evaluated and compared cytotoxic effects between artemisinin derivatives including artemisinin, artemether, artesunate and dihydroartemisinin. A new synthetic drug was also tested. However, further studies are needed to prove its effectiveness through clinical osteosarcoma treatment. In addition, further research is needed to show efficacy, to determine the toxicity of artemisinin and its derivatives, to see whether the use of these small molecules is effective in humans.

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Potential conflicts of interest

None.

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ผลของการทำลายเซลมะเร็งกระดูกชนิดออสติโอซาร์โคม่าด้วยยาต้านมาลาเรียอาร์ติมิซินีนและอนุพันธุ์

ภูริ พันธ์จิรางกูร, พฤษพงศ์ ศรีสวัสดิ์, ทิพชาติ บุณยรัตพันธุ์, ทวีทรง พัฒนาศิลป์, มฑิรุธ มุ่งถิ่น

ภูมิหลัง: *มะเร็งกระดูกชนิดออสติโอซาร์โคม่าเป็นมะเร็งชนิดปฐมภูมิที่พบได้บ่อยมาตรฐานในการรักษาปัจจุบัน ได้แก่ การให้ยาเคมีบำบัดร่วมกับการผ่าตัดรักษาอย่างไรก็ตามภาวะแทรกซ้อนจากยาเคมีบำบัดเกิดขึ้นได้มีการศึกษา รายงานการให้ยาต้านมาลาเรียอาร์ติมิซินีนและอนุพันธุ์สามารถมีผลทำลายเซลมะเร็งและต่อต้านการเกิดใหม่ ของเส้นเลือดที่ไปเลี้ยงมะเร็ง*

วัตถุประสงค์: *การศึกษานี้เพื่อทดสอบการทำลายเซลมะเร็งกระดูกชนิดออสติโอซาร์โคม่าของยาต้านมาลาเรีย อาร์ติมิซินีน และอนุพันธุ์*

วัสดุและวิธีการ: *เซลมะเร็งกระดูกชนิดออสติโอซาร์โคม่า MG63 และ 148B นำมาเพาะเลี้ยงการวิเคราะห์โดยวิธี MTT เพื่อศึกษาผลการทำลายเซลมะเร็งของยาต้านมาลาเรียอาร์ติมิซินีนและอนุพันธุ์ที่เวลา 48 ชั่วโมงโดยมีการใช้ยาเคมีด็อกโซรูบิซินเป็นตัวควบคุมใช้ระดับค่าเฉลี่ยยับยั้ง IC_{50} จากการทดลองทั้งสามครั้งนำมาเปรียบเทียบทางสถิติ เพื่อหาความแตกต่างว่ามีนัยสำคัญโดยใช้วิธี Independent t-test*

ผลการศึกษา: *ยาต้านมาลาเรียอาร์ติมิซินีนและอนุพันธุ์แสดงผลการทำลายเซลมะเร็งกระดูกชนิดออสติโอซาร์โคม่าโดยที่ยา RKA182 ซึ่งเป็นยาที่สังเคราะห์ใหม่มีความสามารถในการหยุดยั้งการเจริญเติบโตของเซลมะเร็งมากที่สุด คุณสมบัติของยาที่สามารถละลายน้ำได้ดีอาจจะเป็นปัจจัยสำคัญในการทำลายเซลมะเร็ง*

สรุป: *ยาต้านมาลาเรียอาร์ติมิซินีนและอนุพันธุ์สามารถยับยั้งการเจริญเติบโตของเซลมะเร็งกระดูกชนิดออสติโอซาร์โคม่า ยา RKA182 มีประสิทภาพสูงสุดควรมีการศึกษาต่อไปในอนาคตเพื่อพัฒนาสังเคราะห์ยาใหม่เพื่อใช้เป็นยาต้านมะเร็งกระดูกชนิดออสติโอซาร์โคม่าต่อไป*