Artemisinin and Its Derivatives in Cancer Care

Healthcare Provider Resource

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Developed by:
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of the Canadian College of Naturopathic Medicine

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General Information

Herbal proper name: *Artemisia annua*

Herbal common name: Sweet wormwood, Qinghao

Extracts: Artemisinin

Derivatives: Artesunate, dihydroartemisinin (artenimiol), artemether

Routes of administration: Oral, intravenous, vaginal suppository, rectal, intramuscular

Common uses in cancer care: Artemisinin and its derivatives are sometimes used in an attempt to achieve improved cancer outcomes including response rates and survival.

Summary

Artemesia annua is a medicinal plant with a long history of use in Traditional Chinese Medicine. Artemisinin is an extract from *Artemisia annua,* and several semi-synthetic derivatives have been developed including artesunate and dihydroartemisinin. Artemisinin and artesunate are approved for use for the treatment of malaria. Interest in the use of artemisinin and its derivatives in cancer has grown due to observed inhibitory and cytotoxic effects on cancer cells lines in vitro. Although several anti-cancer mechanisms of action have been studied, the proposed main mechanism is the intracellular iron-facilitated production of hydroxyl radicals leading to cellular oxidative stress. Oral and intravenous (IV) artesunate are the most common forms and routes used in cancer care. The structured literature search yielded two RCTs, four single-arm trials, and eight case reports evaluating artemisinin or its derivatives for cancer. Treatment was administered orally (n=10), IV (n=3), and by vaginal suppository (n=1). Most studies have used artemisinin as monotherapy, and thus little is known regarding possible interactions with cancer treatments. Although several case reports describe positive outcomes for response and survival, clinical trials have mostly focused on safety, dose, and feasibility. The only randomized controlled trial to assess survival found no difference in overall survival compared to controls in patients with lung cancer. Due to significant heterogeneity and limited research, no overarching statement can be made regarding artemisinin's efficacy as an anticancer agent. Most studies have found artemisinin and its derivates to be safe; however, side effects including anemia, neutropenia, and gastrointestinal disturbances are common. Monitoring at baseline and throughout treatment is recommended for safety. More research is needed to assess the usefulness as artemisinin and its derivatives as a cancer treatment.

Background Information

Artemesia annua is a medicinal plant that has been used in Traditional Chinese Medicine for over 2,000 years.[1] Artemisinin is an extract from *Artemesia annua,* which has been approved for the treatment of malaria since 1986.[2] The discovery of artemisinin for malaria by Tu Youyou was awarded the Nobel Prize in Medicine and Physiology in 2015.[3] Several derivatives of artemisinin have been discovered and studied, the most common of which are artesunate and dihydroartemisinin (the active metabolite).[2] Artemisinin and its derivatives have been studied in various other conditions since its discovery, including viral and parasitic infections, lupus, and diabetes.[3] In recent years, interest in artemisinin and its derivatives for use in cancer care has grown.[2,3] In vitro studies have reported inhibitory and cytotoxic effects of artemisinin on various cancer cell lines.[2]

In Canada, *Artemisia annua* and artemisinin extracts are available as natural health products. Artemisinin is also available as a pharmaceutical, as are the semi-synthetic derivatives including artesunate and dihydroartemisinin. Studies in cancer have focused primarily on the pharmaceutical derivative artesunate.

Methods

Monographs are created by the Patterson Institute for Integrative Oncology Research team and updated every two years, or when significant new literature is published. A comprehensive and structured literature search was completed in Medline and Cochrane Library for artemisinin and its derivatives, and cancer from inception to April 22, 2022. Eligibility criteria included English-language human studies in cancer reporting on efficacy, QoL, safety, or feasibility of using artemisinin and its derivatives among cancer patients. Studies among healthy human populations were included if they commented on safety, PK, or pharmacodynamics, and there were limited studies among cancer populations. A scoping review was performed to identify missing papers and background information. The papers were screened by two reviewers independently. Data was extracted into standardized spreadsheets, and studies summarized using descriptive statistics.

Pharmacokinetics

Pharmacokinetics of artemisinin and its derivatives vary based on route of administration and type of artemisinin or derivative.

Artemisinin itself has low water solubility and bioavailability which limits its effectiveness.[4-6] Semi-synthetic derivatives such as artesunate, artemether, and dihydroartemisinin have improved bioavailability and thus are generally assumed to have greater therapeutic potential.[5] Additionally, new drug-delivery systems such as nano-technology and liposomes are being investigated as ways to further improve absorption and stability.[2] Artemisinin, artesunate, and dihydro-artemisinin are water soluble, whereas artemether is lipid soluble.[5]

Across all routes of administration, artesunate and artemether are rapidly absorbed and converted to the active metabolite, dihydroartemisinin (DHA).[4,6] This metabolism occurs through CYP 2D6 for artesunate, and CYP 3A4 and CYP 3A5 for Artemether.[4] Although artemisinin is metabolized by CYP 2B6 and CYP 3A4 and can produce DHA, it seems, at least based on one study that it produces minimal DHA compared to artesunate and artemether. [7]

The bulk of the research on pharmacokinetics of artemisinin-compounds is on artesunate and DHA. Although pharmacokinetics vary by route of administration, overall artesunate and other derivatives are rapidly absorbed, have short half-lives, and are rapidly converted to DHA.[5,6,8] IV administration produces the greatest plasma concentration.[6]

Oral administration:

Although some sources have reported low oral bioavailability of artesunate,[5] most sources have found quite high bioavailability.[6] A review of 16 studies using oral artesunate found bioavailability of DHA (the active metabolite) to be between 80-85%.[6] The peak concentration of DHA exceeds that of artesunate.[6] Artesunate reaches peak levels on average within an hour,[6] with some studies finding this takes only minutes,[5] while the artemether derivative takes 2-6 hours.[5] Artesunate is metabolized to DHA, reaching peak levels within 2-hours, and has a plasma half life of 1-2 hours.[5,8] High fat and high calorie meals significantly reduce the absorption rate of artesunate.[6] With long-term use of oral artesunate, a 25% increase in elimination clearance has been observed, indicating an autoinduction of metabolism.[8]

IV administration:

IV administration results in a peak plasma concentration greater than any other route.[6] Artesunate rapidly reaches peak concentrations and is quickly metabolized to DHA. The half-life of artesunate is less than 15 minutes. Doses ranging from 1-4 mg/kg achieve peak plasma concentrations in the range of 6,000 to 36,000 ng/mL. Peak DHA concentrations are reached around 25 minutes following artesunate administration with an elimination half-life around 30-60 minutes.[6]

Rectal administration:

Rectal administration of artesunate has about 50% the bioavailability of oral administration.[6] Peak plasma levels are achieved 0.5-1.5 hours after administration, and half-life is around 1 hour. Peak DHA concentration is reached around 1.1-2 hours after administration, with an elimination half-life between 0.8-1.8 hours.[6]

Intramuscular (IM) administration:
IM artesunate produces high bioavailability, however not as high as with IV administration. The artesunate half-life is slightly longer when given IM as compared to IV. Otherwise, pharmacokinetics are very similar to the IV route.[6]

In children, weight is a significant variable in pharmacokinetics.[6] Using weight-based dosing is recommended.

Mechanism of Action

Artemisinin and its derivatives have various mechanisms of action which are quite complex. In cancer, artemisinin-compounds' effects include antiproliferative, proapoptotic, induction of cell cycle arrest, antiangiogenic, induction of oxidative stress, autophagy, ferroptosis, impacts on oncogenes and tumor suppressor genes, induction and suppression of cell signaling pathways, and effects on multidrug resistance.[2,9]

The key purported mechanism of artemisinin is the cleavage of the endoperoxide bridge.[2,10] This step is facilitated by intracellular iron, and results in the formation of oxygen and alkylating carbon radicals (mostly hydroxyl radical, -OH), which causes oxidative damage.[10] The oxidative stress contributes to cell cycle arrest, anti-angiogenesis, apoptosis, autophagy, and ferroptosis. Cancer cells are more susceptible to the effects of artemisinin due to their higher intracellular iron levels and higher O^2 : H^2O^2 ratio.[2] Furthermore, cancer cells have reduced expression of antioxidant enzymes making them more susceptible to the effects of reactive oxygen species (ROS).[2,10]

Several key cell signaling pathways can be altered by artemisinin compounds, contributing to their anticancer effects. Affected signaling pathways include: PI3K-Akt, T-cell receptor, toll-like receptor, TGF-beta, and insulin signaling.[2]

Lower doses of artemisinin are more likely to induce cell cycle arrest, whereas high doses may induce apoptosis.[2]

A detailed discussion on mechanism of action can be found in this excellent review paper by Bhaw-Luximon & Jhurry.[2]

Clinical evidence related to effectiveness

There are 14 studies (16 publications) related to the use of artemisinin and its derivates on cancer outcomes including safety, survival, tumor response, tumor markers, and quality of life. Of those, there was 1 randomized, placebo-controlled trial (RCT), 1 non-placebo-controlled RCT, 4 single-arm clinical trials (published in 6 reports), 1 case series, and 7 case reports. Table 1 summarizes the findings of the clinical trials. Due to limited data and significant heterogeneity, it isn't possible to make an overall statement regarding the efficacy of artemisinin and its derivatives on cancer. However, there is promise for anticancer activity as outlined in the described studies, and further research is warranted.

Oral administration

Most clinical trials and case reports using oral treatment have used artesunate; however, one single-arm trial used dihydroartemisinin,[11] one case series[12] and three case reports[13-15] used artemisinin, and one case report used artemether.[16]

The only randomized, double-blind, placebo-controlled trial of artesunate in cancer evaluated the effect of 200 mg of oral artesunate therapy daily for 14 days prior to surgery in 23 people with mixed stages of colorectal cancer.[17] The primary outcome was the proportion of tumor cells undergoing apoptosis (a priori defined as

clinically significant if >7% on Tunel staining). Secondary outcomes included the effect on tumor markers EGFR, c-MYC, CD31, Ki67 and p53, and clinical responses. There was an increase in cells undergoing apoptosis in the treatment arm compared to the placebo arm (67% vs 55%, respectively), however statistical analysis was not applied. There were no marked differences between groups for most secondary tumor marker analyses, except for reduced Ki67 staining. During a median follow up of 42 months, there were 6 recurrences in the placebo group and 1 in the artesunate group, which resulted in a non-significant hazard ratio of 0.16 (95% CI 0.02-1.3). CEA was measured in a subset of patients; no patients in the artesunate group had a rise in CEA whereas 3 in the placebo group did ($p = 0.03$). Treatment was well tolerated with 2 cases of neutropenia and anemia, and one case of nausea possibly related to artesunate.

A phase 1 study evaluated oral artesunate in 23 women with heavily pre-treated metastatic breast cancer, and published their findings in three publications.[18-20] Patients received either 100 mg, 150 mg, or 200 mg daily for 4 weeks alongside standard oncological treatment. The initial publication reported on toxicity and response rates.[18] There were a total of six dose-limiting toxicities experienced by three patients, which included leukopenia, neutropenia, anemia, and asthenia. There were 65 grade 1 and 2 adverse events, 86% of which resolved by the last study visit at 8-weeks. Hematological adverse effects (AEs) were the most common (anemia, neutropenia, leukopenia). The risk of DLTs did not exceed 33% at any dose level, thus the maximum tolerated dose was not reached. The authors recommend 200 mg/day for future clinical trials. Response rate was evaluated in 15 patients; 10 had stable disease and none had partial or complete responses. A long-term follow-up of this study was published two years later,[19] which reported on 13 patients who continued artesunate therapy for a combined total of 3825 treatment days. A total of 25 AEs grade ≥ two possibly related to artesunate were documented; AE frequencies were at two, six and 17 within the dose groups 100, 150 and 200 mg/d respectively. Six of these AEs were classified as grade 3 and included thrombosis, neutropenia, diarrhea, and anemia. The authors concluded that artesunate dosed at 200 mg/day for 1115 cumulative treatment days (37 months) resulted in no major safety concerns. Finally, a third publication looked specifically at audiological adverse effects associated with artesunate.[20] Five patients had non-dose-limiting AEs concerning the auditory system (subclinical hearing loss and tinnitus) during the 4-week trial and another one after 11 months of continued therapy. Although there were no dose-limiting audiological AEs, six patients developed AEs related to the vestibular system (vertigo); four occurred during the first four weeks (1 which was a dose-limiting serious adverse event (SAE), fully recovered after discontinuation of artesunate) and two after two and 10 months. Monitoring for auditory AEs should be considered in ART administration, particularly for long-term use.

One single-arm trial administered dihydroartemisinin (also called Artenimol) to 10 patients with stage III/IV cervical cancer.[11] Patients were administered 100 mg daily for the first week, and 200 mg daily for weeks 2-4; no other cancer treatment was administered. Symptoms resolved for all nine patients who had baseline symptoms (primarily pain and vaginal bleeding) and termed this "clinical remission". There were no grade 3-4 adverse events, grade 1-2 adverse events were reported in 5/10 patients and included flu-like symptoms, headache, and abdominal pain. Biopsy samples taken at baseline, day 14 and day 28 revealed down-regulation of p53, EGFR, Ki-67 and CD31, and increased expression of CD71. Based on imaging there were no objective tumor responses. Authors reported that survival time was superior to those typically reported at their institution. Caution is warranted when interpreting these results as this appeared to be a low resource setting with no available treatment for advanced cervical cancer which is not the case in North America.

One case series and five case studies reported on oral use of artemisinin or derivatives in cancer. A retrospective case series examined the safety and efficacy of oral artemisinin in patients with prostate cancer.[12] Artemisinin was administered at a dose of 300-400 mg 3x/day every other week for 3-24 months (median 9.5 months, IQR 5-12 months) in 15 patients. All patients received additional natural therapies as per the treating

naturopathic doctor. Of the patients who had previously undergone radical prostatectomy and had a biochemical recurrence, 2/5 (40%) had improved PSA kinetics (PSA doubling time and/or PSA velocity) after artemisinin therapy. Of those with no prior radical prostatectomy, 5/10 (50%) had improved PSA kinetics. No patients developed signs of metastasis, no patients died, and no adverse effects were reported.

A case report described an 80-year-old with a metastatic Gleason 8 prostate cancer who appeared to have a transitory response to treatment with artemisinin.[13] Upon diagnosis, the patient had a PSA level of 580 ug/L and skeletal metastases. He was treated with 2 weeks of bicalutamide at 50 mg/day. Two months post-diagnosis he started on 200-250 mg/day oral artemisinin. PSA was < 2ug/L a few weeks later, and imaging showed a 50% reduction in the prostate tumor and regression of the skeletal metastasis. However, PSA started to rise again and by 10-months post initiation of artemisinin it was 1245 ug/L, and imaging showed increased growth of the skeletal metastases. At this time, the patient switched to IV artesunate at a dose of 150 mg twice weekly. He did not respond to this treatment and died about 4 months later (15-months post diagnosis). Treatment with artemisinin was well tolerated. Although the authors report these results in a favorable light, it is important to acknowledge that the short-term bicalutamide treatment may have had the more pronounced effect. It is also not clear if the 15-month survival this patient experienced is noteworthy.

A case report of a 75-year old male with a pituitary adenoma reported symptom resolution with the use of an artemisinin analogue, artemether.[16] The patient presented with a 2.4 x 2.6 cm macroadenoma of the pituitary with vision and hearing loss and gait abnormalities. The patient refused surgery and radiation and started oral artemether at a dose of 40 mg/day (approximately 0.5 g/kg). After 1 month, the treatment was reduced to every other day for and additional month, then dropped to 2x/week for 10 months. The patient also took 500 mg of vitamin C and vitamin E daily. A CT scan at 4 months showed a slight increase in size of the adenoma, but the patient reported a reduction in all symptoms. Repeat CT scans at 9 and 19 months showed stability in size, and reduced density of the lesion from 72-77 HU to 51-59 HU. The patient reported a near complete resolution of symptoms. The authors hypothesized that the decreased density indicated a treatment response and may have reduced pressure on the optic nerve and surrounding structures resulting in the observed symptom relief.

One report described the treatment of two patients with metastatic uveal melanoma with artesunate.[21] Both patients had progressed despite standard chemotherapy treatment when artesunate was added to their plan. The full text of this paper could not be obtained, and thus only limited details are available. The authors report a transient response in one patient who was also treated with fotemustine, and an objective response to splenic and lung metastasis in a patient treated with dacarbazine. The latter patient was still alive 47-months post diagnosis of metastatic disease, which the authors noted as far superior than typical. Information on route of administration and dose for the artesunate was not available.

A case report described a 62-year-old with heavily-pretreated metastatic adrenocortical carcinoma (ACC) who experienced a partial response lasting about 12 months with the use of *Artemisia annua* (99% artemisinin).[14] The patient had been treated over the course of 9-years with surgery, mitotane, cytotoxic chemotherapy, and radiation prior to initiating artemisinin at a dose of 600 mg daily for 5 days, followed by 5 days off. The treatment was well tolerated with no side effects. Two-months after artemisinin initiation, MRI showed reduction in size of two liver metastases, which was maintained at a scan 6-months later. The patient continued the same protocol of artemisinin for almost 9 months. After which, artemisinin was discontinued for about 6 months due to the patient developing a herpes zoster infection on their abdomen. After discontinuing artemisinin, an MRI 3-months later showed an interval increase in the size of several hepatic metastases. The patient re-started artemisinin but disease continued to progress, however slowly, and the patient maintained a good quality of life. Overall, the authors noted that the patient experienced a response of about 12-months with use of artemisinin.

Two case reports described possible safety concerns with the application of oral artesunate or artemisinin. The first described potential hepatotoxicity in a patient with glioblastoma multiform (GBM) treated with artesunate. The patient was treated with surgery and intraoperative radiotherapy followed by radio-chemotherapy with temozolomide.[22] The patient self-administered oral Artesunate (200 mg/d) and Coptis-Kush (Rhizoma Coptidis chinensis; Herba Siegesbeckiae orientalis; Herba Artemisiae scopariae H; Radix Dictamni dasycarpi) for 2.5 weeks before discontinuing due to elevated liver enzymes and symptoms including weight loss, heartburn, nausea, weakness, and depressive mood. After discontinuation of both artesunate and Coptis-Kush, liver parameters returned to normal, and symptoms resolved. As the patient was on several medications which can cause hepatotoxicity, including temozolomide, the causative agent could not be determined. However, the authors felt that caution is warranted when using artesunate alongside other hepatotoxic medications. The second case report outlined possible neurotoxicity caused by artemsinin in a women post-surgery for early-stage breast cancer.[15] The woman was taking 200 mg of artemisinin twice daily, in addition to another herbal combination product, tamoxifen, and fluoxetine. The woman presented to the hospital with diplopia, dysarthria, and ataxic gait. Brain magnetic resonance imaging (MRI) showed symmetric punctate foci of T2 signal prolongation. Upon discontinuation of her herbal products including the artemisinin, the woman experienced rapid resolution of symptoms and improvement in repeat brain MRI. Based on a review of the other herbal products, it was deemed artemisinin was the likely cause.

Intravenous administration

Artesunate is the only form that has been studied for intravenous use. One RCT evaluated IV artesunate in patients with advanced non-small cell lung cancer (NSCLC) receiving cisplatin-vinorelbine chemotherapy.[23] The paper was published in Chinese language, and only the abstract was translated into English and available for review. Patients were randomized to chemotherapy alone (n = 60) or chemotherapy plus IV artesunate (n = 60). Artesunate was given at a dose of 120 mg/day for the first 8 days of the 21-day chemotherapy cycle. At least 2 cycles of treatment were administered. Although the Artesunate group had a higher disease control rate (88.2% vs 72.7%, $P < 0.05$) and time to progression (24 vs 20 weeks, $P < 0.05$), no significant differences were found in short-term survival, mean survival, or 1-year survival. There was no significant difference in toxicity between the two groups.

A phase I dose escalation trial evaluated safety, pharmacokinetics, and response rates of IV artesunate in patients with advanced refractory solid tumors.[24] Nineteen patients were administered artesunate on days 1 and 8 on a 21-day cycle with dose escalation levels of 8, 12, 18, 25, 34, and 45 mg/kg. 18/19 participants were analyzed for toxicity. The maximum tolerated dose (MTD) was determined to be 18 mg/kg, after 1/6 patients experienced dose limiting toxicities (DLT) at both the 12 mg/kg and 18 mg/kg doses, whereas 2/2 patients had a DLT at 25 mg/kg. DLTs included neutropenic fever, hypersensitivity reaction, liver function abnormality, and nausea/vomiting. Many non DLTs were recorded including anemia, neutropenia, gastrointestinal side effects (e.g. diarrhea, constipation, nausea/vomiting), elevations in LFTs, fatigue, loss of appetite, electrolyte imbalances, hypoalbuminemia, arthralgias, dizziness, headache, and cough. Pharmacokinetic analysis demonstrated a short half-life of ART (Tmax=5 min; T1/2=7–8 min) and rapid metabolism by esterase-catalyzed hydrolysis to its active metabolite, DHA. DHA had a Tmax of 20min, and median half-life of 30 minutes to 3.5 hrs which increased with dose. 15/19 patients were evaluated for response; 4/15 had stable disease, there were no partial or complete responses.

A case report of a man with glioblastoma multiform (GBM) treated with IV DCA and artesunate raised safety concerns following liver and bone marrow toxicity.[25] Following disease progression after surgery and radio-chemotherapy, the 52-year-old man received IV DCA (unknown dose) and artesunate (2.5 mg/kg). Hepatic and bone marrow toxicities occurred a few days after infusion. The patient received supportive treatment

in hospital; however, his condition deteriorated, and he died ten days after receiving the combined treatment. The Roussel Uclaf Causality Assessment Method scoring system revealed reasonable probability that the combination of DCA and ART induced liver injury.

Vaginal suppository administration

Artesunate vaginal suppositories may promote histological clearance of Cervical Intraepithelial Neoplasms (CIN) II and III based on a small phase I trial.[26] This dose-finding study treated 28 women with varied doses and durations of treatment; group 1 used 50 mg artesunate for 5 consecutive nights in a 14-day cycle, groups 2-4 used 200 mg artesunate for 1, 2, and 3 14 day cycles respectively. Assessments were performed at 15, 28, and 41 weeks. Histologic regression to CIN 1 or less was observed in 67.9% (19/28) of participants (42% at week 15). Clearance of HPV occurred in 47.4% of subjects whose lesions underwent histologic regression and in none of the patients who did not have a regression. The rates of regression were similar across groups, but the time to regression was longer in groups receiving only 1 treatment cycle. The authors report that these results are better than the natural course of disease, which has found regression rates to be 20-29% at 15 weeks. While there were no grade 3 or 4 adverse events, there were a fair number of grade 1 and 2 local and systemic events. The following were reported in 5 or more participants: vaginal pruritus (n=13), vaginal pain (n= 12), vaginal discharge (n= 8), vaginal spotting (n= 6), uterine cramping (n = 6), gastrointestinal discomfort (n=9), dizziness (n=9), headache (n=11), and vaginal yeast infection (n =6).

Safety and adverse events

In clinical research, artesunate and its derivatives have generally been safe and reasonably well tolerated; however, adverse events are common, and monitoring is recommended. This therapy should only be used under the guidance of a qualified health care provider.

Although artesunate is used for the treatment of severe malaria with a good safety profile, the dosing for malaria is only 2.4 mg/kg given IV in 4 doses over 48 hours.[27] This short-term use is generally well tolerated, but side effects can include anorexia, dizziness, light headedness, taste alteration, nausea, diarrhea, reversible decrease in reticulocyte count, increased liver enzymes, bradycardia, heart block, rare allergic reactions (e.g., urticaria, pruritis, dyspnea), and delayed hemolytic anemia. In Canada, it is recommended to monitor for hemolytic anemia via a complete blood count weekly for 4 weeks following use, and they advise patients to monitor for symptoms of hemolytic anemia such as dark urine, jaundice, fever, abdominal pain, shortness of breath, or chest pain.[27]

Data specific to cancer and different routes of administration are described below.

Oral:
At doses up to 200 mg daily, artesunate is considered safe and well tolerated, however several side effects have been reported in clinical trials.[17-20] The most common side effects are anemia, neutropenia, and gastrointestinal disturbances (e.g. diarrhea and nausea). Other reported side effects include leukopenia, asthenia, thrombosis, vertigo, subclinical hearing loss, and tinnitus. While most side effects have been mild, reported dose-limiting or grade $\geq$3 toxicities include leukopenia, neutropenia, anemia, thrombosis, diarrhea, and asthenia.[18,19] Adverse events may be more common at higher doses, such as 200 mg/day compared to lower doses.[19] Case reports have reported neurotoxicity (diplopia, dysarthria, ataxic gait) when used in combination with another herbal product, tamoxifen and fluoxetine,[20] and hepatotoxicity at a dose of 200 mg/d alongside Coptis-Kush.[22]

There is insufficient data on side effects with artemisinin, dihydroartemisinin, and artemether. One small open-label study using 200 mg dihydroartemsinin reported only grade 1 and 2 adverse events including flu-like symptoms, headache, and abdominal pain.[11]

Intravenous:

Reported dose limiting toxicities (DLT) include neutropenic fever, hypersensitivity reaction, liver function abnormality, and nausea/vomiting, which were mostly reported at doses of 12 mg/kg and above.[24] Non-DLTs are similar to those reported with oral use, including anemia, neutropenia, gastrointestinal side effects, elevations in LFTs, fatigue, loss of appetite, electrolyte imbalances, hypoalbuminemia, arthralgias, dizziness, headache, and cough.[24]

IV DCA combined with artesunate (2.5 mg/kg) should be avoided due to a risk identified in a case for potential fatal liver and bone marrow toxicity.[25]

Suppository:
Adverse events reported from a single study include vaginal pruritus, vaginal pain, vaginal discharge, vaginal spotting, uterine cramping, gastrointestinal discomfort, dizziness, headache, vaginal yeast infection.[26] Less commonly reported adverse events included vaginal dryness, pelvic pain, perineal pain, dyspareunia, short-term tinnitus, bacterial vaginosis, vaginal inflammation, urinary tract infection, and noninfective cystitis.

Interactions with other Therapies

Data is limited on the use of artemisinin and its derivatives with other cancer therapies. Most studies to date have used these treatments as monotherapy.

Chemotherapy:

There are no studies combining oral artemisinin or its derivatives with chemotherapy. IV artesunate has been used alongside cisplatin-vinorelbine chemotherapy for patients with advanced lung cancer resulting in superior disease control rates and time to progression indicating that a negative interaction between these therapies is unlikely.[23]

Various preclinical studies have indicated the potential for a synergistic anti-cancer effect with combined artemisinin and chemotherapy drugs, including doxorubicin, cisplatin, carboplatin, temozolomide, and cytarabine.[28]

Radiation therapy:

There are no clinical studies combining oral, IV, or suppository forms of artemisinin or its derivatives with radiation therapy. Therefore, there is no available data to comment on a possible interaction. Limited preclinical data suggests a radio-sensitizing effect of artemisinin compounds in various cell lines.[28]

Other cancer therapies:

Preclinical data has demonstrated potential synergic tumor-inhibiting activity between artesunate and erlotinib, bortezomib, thalidomide, lenalidomide, and rituximab.[28] There is no clinical data available.

Due to immunosuppressive effects of artemisinin and derivatives, a negative interaction with immunostimulant therapies such as PDL1/PD1 and CTLA4 inhibitors is possible, although this has not been studied.

Cytochrome P450 metabolism and P-glycoprotein:

Artemisinin and derivatives are metabolized in the liver primarily by isozymes CYP2A6, 2B6, and 3A4.[28] The effect of artemisinin and derivatives on cytochrome P450 enzymes has been evaluated in healthy subjects following oral administration.[29] Artemisinin and derivatives induced CYP3A and CYP2C19 activity. CYP 1A2 was inhibited by derivatives but induced by artemisinin, and CYP 2D6 was inhibited after 1 day of oral administration but on day 5 had increased. The magnitude of effects were considered low to moderate, and may not have large therapeutic implications in the general population.[29]

A review of preclinical trials evaluated the impact of artemisinin on P-gp.[30] The authors found that commonly used artemisinin derivatives are not transported by P-gp, but many artemisinin derivatives act as P-gp inhibitors, which indicates the potential to reduce multi-drug resistance induced by P-gp.

Cautions and Contraindications

Data on cautions and contraindications from clinical trials is limed. The following are commonly considered to be relative or absolute contraindications by integrative practitioners using artesunate and derivatives based on theoretical concerns or extrapolation of data in other populations.

Caution is recommended for patients with G6PD deficiency, as oxidative therapies such as artesunate may increase the risk of hemolytic anemia.[31]

Artesunate is not recommended in patients with severe liver impairment due to its hepatic metabolism and data from a phase I study which noted elevations in alanine transaminase.[24] Similarly, caution is warranted in patients taking other hepatotoxic medications.

Caution is warranted in those with hemochromatosis due to a theoretical concern regarding increased damage caused by high iron stores, particularly on the liver. This is due to artemisinin's intracellular iron-facilitated production of hydroxyl radicals leading to oxidative stress.

Due to artemisinin's ability to cause anemia and leukopenia, caution is warranted in patients with these conditions at baseline. Similarly, clinicians should be cautious when combining artemisinin and derivatives with myelosuppressive cancer treatments due to the risk a patient has their cancer treatment discontinued as a result of increased myelosuppression, which could inadvertently lead to worse cancer outcomes.

Caution is recommended for patients on immunostimulant medications, including immunotherapy (PD1/PDL1 inhibitors) as theoretically artemisinin and derivatives may interact due to reported immunosuppressant effects, although data on this is not available.

IV administration of Artesunate in conjunction with IV DCA should be avoided until more is known due to potential liver and bone marrow toxicity.[25]

Due to lack of evidence, the use of artemisinin and its derivatives are not recommended during pregnancy or lactation in cancer populations. Although IV artesunate is used for the treatment of severe malaria in the second and third trimester (IV quinine is preferred for the first trimester),[27] this cannot be applied to cancer care for several reasons. The dose and duration of use in malaria is typically lower and shorter than what is used in cancer care. IV artesunate is an effective treatment for severe malaria, whereas its impact in cancer care is still uncertain. Finally, the risk of untreated severe malaria is significant, and thus the risk to benefit ratio favors treatment in that scenario. Similarly, although the dose of artemisinin that passes in to breast milk is low and not suspected to pose harm,[32] given the uncertain benefit of artesunate in cancer the combination is likely best avoided.

Regular monitoring is recommended for all patients on artesunate therapy. Recommended baseline testing includes complete blood count (CBC), G6PD testing, liver function tests, creatinine, and ferritin. Monthly follow up with at minimum a CBC, liver function tests, and creatinine are recommended. Additionally, symptoms and signs for AEs should be monitored by a clinician regularly.

Dosing, frequency and length of treatment

Oral:

Artesunate: Clinical trials and case reports of oral artesunate previously described have used daily doses ranging from 100-250 mg daily, with 200 mg being most common. Most studies have been short-term, in the range of 2-4 weeks. However, one study[19] and one case report[21] have used daily dosing for several months.

Artemisinin: Research is limited, but doses have typically been higher than those used for artesunate, ranging from 200 mg/day to 400 mg 3x/day. The case series which used up to 400 mg 3x/day dosed it every other week.[12] In the same case series, artemisinin was used for up to 24 months.

IV:

Artesunate: Dosing for IV artesunate is less consistent than with oral use. While one dose escalation trial found

the maximum tolerated dose to be 18mg/kg,[24] this is significantly higher than what has been used in the only other clinical trial (120 mg),[23] and what is used for malaria (2.4 mg/kg). In practice, based on communications with clinics using artesunate for cancer, a dose of 2.4 mg/kg is commonly used (e.g. 168 mg for a 70 kg adult). Frequency of infusions also varies, but typically includes treatment breaks. In practice, based on communications with clinics using artesunate for cancer, administering it 1-2 times/week for 2 weeks followed by a week off is common.

Only artesunate has been studied and used intravenously.

Other derivatives and routes of administration:

Vaginal suppositories of artesunate have been used at a dose of 200 mg/day for 5 days, repeated every 2 weeks for 1-3 cycles.[26] Oral artemether was used in one case report at a dose of 40 mg (0.5mg/day).[16]

Disclaimer

This monograph provides a summary of available evidence and neither advocates for nor against the use of a particular therapy. Every effort is made to ensure the information included in this monograph is accurate at the time it is published. Prior to using a new therapy or product, always consult a licensed health care provider. The information in this monograph should not be interpreted as medical advice nor should it replace the advice of a qualified health care provider.

Table 1: Prospective clinical trials of artemisinin and derivatives for cancer

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Jansen et al, 2011[11]	Single-arm trial	Cervical cancer – stage III/IV N = 10	**Form:** Artenimol **Route:** Oral **Dose**: 100mg for 1 week, then 200mg for 3 weeks **Frequency and duration**: daily for 4 weeks	N/A	Clinical response (which appeared to be measured based on presence/absence of symptoms) Objective response (imaging) Tumor markers in biopsy sample Adverse events	Symptoms resolved for all nine patients who had baseline symptoms (primarily pain and vaginal bleeding). This was considered "clinical remission". Objective responses: None Adverse events: Grade 3-4: none Grade 1-2: reported in 5/10 patients and included flu-like symptoms, headache, and abdominal pain. Biopsy samples (baseline, day 14 and day 28): Down-regulation of p53, EGFR, Ki-67 and CD31, and increased expression of CD71
Krishna et al, 2015[17]	RCT	Colorectal cancer – surgically resectable N = 23 Patients were awaiting surgery	**Form:** Artesunate **Route:** Oral **Dose**: 200 mg **Frequency and duration**: daily for 14 days prior to surgery	Placebo	Primary outcome: proportion of tumor cells undergoing apoptosis (a priori defined as clinically significant if >7% on Tunel staining). Secondary outcomes: effect on tumor markers EGFR, c-MYC, CD31, Ki67 and p53, CEA, and clinical responses.	Apoptosis: Increase in cells undergoing apoptosis in the treatment arm compared to placebo (67% vs 55%) (no statistical analysis applied) Tumor markers: No differences between groups for most secondary tumor marker analyses, except for reduced Ki67 staining. CEA was measured in a subset of patients; no patients in the artesunate group had a rise in CEA whereas 3 in the placebo group did ($p = 0.03$)

						Clinical responses: During a median follow up of 42 months, there were 6 recurrences in the placebo group and 1 in the artesunate group, hazard ratio = 0.16 (95% CI 0.02-1.3).
Zhang et al, 2008[23]	RCT (Abstract-only was reviewed)	Lung cancer - advanced N = 120 (60 in treatment arm, 60 in control)	**Form:** Artesunate **Route:** IV **Dose**: 120 mg **Frequency and duration**: daily for the first 8 days of a 21 day cycle, minimum 2 cycles **Concomitant treatment:** Cisplatin-vinorelbine chemotherapy	Cisplatin-vinorelbine chemotherapy alone	Disease control rate TTP Survival (short-term, mean, 1-year)	Disease control and TTP: Artesunate group had a higher disease control rate (88.2% vs 72.7%, P < 0.05) and longer TTP (24 vs 20 weeks, P < 0.05) Survival: No difference in survival measures observed
Deeken et al, 2018[24]	Phase I dose escalation trial	Advanced refractory solid tumors N = 19	**Form:** Artesunate **Route:** IV **Dose**: dose escalation levels of 8, 12, 18, 25, 34, and 45 mg/kg **Frequency and duration**: days 1 and 8 of a 28 day cycle	N/A	Safety including maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) Pharmacokinetics Response rates	Safety: MTD was 18mg/kg DLTs: neutropenic fever, hypersensitivity reaction, liver function abnormality, and nausea/vomiting. Non DLTs: anemia, neutropenia, gastrointestinal side effects (e.g. diarrhea, constipation, nausea/vomiting), elevations in LFTs, fatigue, loss of appetite, electrolyte imbalances, hypoalbuminemia, arthralgias, dizziness, headache, and cough. Pharmacokinetics: ART: short half-life (Tmax=5 min; T1/2=7 to 8 min) and rapid metabolism by esterase-catalyzed hydrolysis to its active metabolite, DHA. DHA: Tmax = 20min, and median T1/2 = 30 minutes to 3.5 hrs which increased with dose. Response rates: 15/19 patients were evaluated for response; 4/15 had

						stable disease, there were no partial or complete responses.
Von Hagens et al, 2017[18]	Phase I single-arm	Breast cancer – heavily pre-treated, metastatic N = 23	**Form:** Artesunate **Route:** Oral **Dose**: 100 mg, 150mg, 200 mg **Frequency and duration**: daily for 4 weeks	N/A	Toxicity Response rates	Toxicity: 6 dose-limiting toxicities (DLTs): leukopenia, neutropenia, anemia, asthenia 65 grade 1-2 AEs: hemotological were most common (anemia, leukopenia) MTD was not reached Response rates (evaluated in 15 patients): 10/15 had stable disease, no partial or complete responses
Konig et al, 2016[20]	Additional publication from Von Hagens et al, 2017	As above	As above	As above	Audiological adverse effects	no dose-limiting audiological effects. Five patients had non-dose-limiting AEs concerning the auditory system (subclinical hearing loss and tinnitus) -four during the 4-week trial and another one after 11 months of continued therapy. Six patients developed vertigo originating from the vestibular system.
Von Hagens et al, 2019[19]	Long-term follow-up of the phase I single-arm trial described above (von Hagens et al 2017)	N = 13	As above except duration was longer but not clearly specified (authors reported there were 1115 cumulative treatment days or 37 months).	As above	Safety	25 AEs grade ≥ 2 possibly related to artesunate were documented; two, six and 17 in dose groups 100, 150 and 200 mg/d respectively. Six of these AEs were classified as grade 3 and included thrombosis, neutropenia, diarrhea, and anemia.

Legend: ART = artesunate, AE = adverse events, bw = body weight, CEA = carcinoembryonic antigen, CR = complete response, DHA = dihydroartemisinin, DLT = dose limiting toxicity, EGFR = estimated glomerular filtration rate, LFTs = liver function tests, MTD = maximum tolerated dose, ORR = overall response rate, OS = overall survival, PFS = progression free survival, PK = pharmacokinetics, PR = partial response, QoL = quality of life, RCT = randomized controlled trial, SE = side effect, SD = stable disease, TTP = time to progression

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