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Methods

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 stressa0 0 91251 0 04(n)] TJETQ[( )] TJET 792 re92 reW*nBT/F20 G[( )] T1a00

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( )11(a)9 neutropenia

naturopathic doctor. Of the patients who had previously undergone radical prostatectomy and had a biochemical recurrence, 2/5 (40%) had improved PSA kinetics (PSA

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-

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

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

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 interactt0 g0 G[(m)-4(a)9(y)-10(i)17(nt)-4(e)9(r)7(a)9(c)9(t)-4(t0 g0 G[(m)-4(a)9(y)-10(i)17(nt

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 common

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 ($p = 0.03$)

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