First Study of Oral Artenimol-R in Advanced Cervical Cancer: Clinical Benefit, Tolerability and Tumor Markers

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Abstract. *Background/Aim: Artenimol-R is cytotoxic in transformed cervical cells and safety in humans is yet to be established. The present study investigates the clinical benefits, safety and the tumor marker effect of orally administered Artenimol-R in patients with advanced cervix carcinoma. Patients and Methods: Ten patients were treated with Artenimol-R for 28 days. Clinical symptoms, vaginal discharge and pain were followed-up. Adverse events were recorded. Biopsy samples were analyzed by immunohistochemistry for the expression of relevant tumor markers. Results: Artenimol-R treatment induced clinical remission with a median time for the disappearance of the symptoms being 7 days. No adverse events of grade 3 or 4 occurred. The expression of p53, Epidermal growth factor receptor (EGFR), and antigen Ki-67 as a cellular marker of proliferation, as well as the number of blood vessels stained by the CD31 antibody decreased, whereas the expression of transferrin receptor protein 1 (CD71) increased. Conclusion: The current pilot study provides evidence on the improvement of the clinical symptoms and the good tolerability of Artenimol-R in patients with advanced carcinoma of the cervix uteri. A survival trial with Artenimol-R in advanced patients is warranted.*

Cervical cancer is the second most common cancer in women worldwide (1). In developing countries, cervical cancer represents the primary cause of cancer-related female deaths The major risk factor for cervical cancer is infection by the human papillomavirus (HPV) (2, 3). In developed countries, screening with the Papanicolaou cervical smear test (Pap-test) detects metaplasia or early cancer development *in situ*. Subsequent cauterization and surgical measures can remove metaplastic and cancerous cells. These measures, however do not establish the risk of progression of cervical cancer in many cases. Implementation of vaccination programs for HPV are expected to lead to reduction of the incidence of cervical cancer. However, in many developing countries vaccination programs are not readily available for massive application. Without national screening or vaccination programmes, cases of cervical cancer in Africa are frequently presented in late stages of progression with symptoms of vaginal bleeding and pain (1, 3). Metastasized *cervix uteri* carcinoma is a devastating disease without effective treatment, leading to death within a few months after diagnosis. None of the currently available oncologic therapies have a convincing impact on the course of the disease (4). The primary tumor is locally invasive and frequently progresses towards the ureters, blocking urinary flow and leading to progressive renal insufficiency, with a fatal outcome in most women (5). A multivariate analysis of prognostic variables in patients with locally advanced disease, identified para-aortic and pelvic lymph node status, tumor size, patient age, performance status, bilateral disease and clinical stage as variables significant for progression-free interval and subsequent survival (6). Artesunate and dihydroartemisinin (DHA), the active metabolite of Artesunate, are proved to possess anticancer activity in the human cervical cancer cell line HeLa, with a half maximal inhibitory concentration (IC_{50}) value of 38.6±4.3 μM and 15.7±3.7 μM, respectively (7). In the same study, Artesunate and DHA inhibited angiogenesis in a dose-dependent manner in the range of 12.5-50 μM and 2.5-50 μM, respectively. Disbrow *et al*. (2005) showed the strong cytotoxic effects on HPV-immortalized and transformed cervical cells *in vitro*, with little effect on normal cervical epithelial cells. DHA and Artesunate induced cell death-involved activation of the mitochondrial caspase pathway with

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resultant apoptosis. The apoptosis was p53-independent and was not the consequence of drug-induced reductions in viral oncogene expression. DHA was applied as the topical treatment of mucosal papillomavirus lesions in dogs, resulting in strongly inhibited viral-induced tumor formation (8).

Artenimol-R, the hemi-succinate ester of artenimol, has an excellent safety profile when used as an antimalarial drug (9, 10). Since there are no alternative therapies available for women in Abidjan, of the Ivory Coast, with advanced cervical cancer, we undertook a pilot clinical pharmacological study in ten patients with stage III and IV cervical carcinoma. The primary objective was to assess the potential clinical benefit of artenimol-R treatment in the patients treated for a restricted period of time. The secondary endpoint was tolerability to the therapy. Clinical symptoms, safety and histological markers of tumor response were initially monitored during the initial 28-day treatment period and follow-up was maintained subsequently.

Table I. *Patient baseline characteristics and treatment onset, clinical relapse and survival.*

Baseline characteristics				Follow up	
Patient number	Age	Tumor stage (FIGO)	Initial clinical symptoms (months)	Time to clinical relapse	Alive in August 2010
1	53	IVA	P/VD	6	No
2	58	IIIB	-	R	Yes
3	70	IIIB	P/VD	7	No
4	52	IVA	VD	8	Yes
5	66	IIIB	VD	8	Yes
6	60	IIIA	P/VD	6	No
7	39	IVA	VD	4	No
8	57	IVA	P/VD	R	Yes
9	69	IVB	P/VD	R	Yes
10	52	IIIB	P/VD	R	Yes

P, pain; VD, vaginal discharge; R: in remission in August 2010.

Patients and Methods

Study design. This was an open-label single-center study, designed to provide evidence for the potential of a novel drug, and to assess its safety and potential clinical benefit in relation to the indication of advanced cervical carcinoma. Ten patients were enrolled in the study and were given a unique patient number (001-010). An initial treatment phase of 28 days was followed by a follow-up phase. The primary endpoint of the study was the recording of the clinical symptoms of the disease over a period of one month and, in cases of clinical success, to evaluate the time of remission or the time to relapse. The secondary endpoint was to establish the adverse event profile. Since obtaining biopsies was straightforward in these patients, the analysis of the tumor by immunohistochemistry was added only as an exploratory endpoint. During the follow-up phase, patients were given the possibility of entering into a second treatment period after the symptoms of pain or abnormal vaginal discharge had recurred. Patients undergoing a second treatment period received 200 mg/day for another 28 days. After this, there was no further treatment but patients were followed-up until their death.

Non-pregnant females older than 18 years were eligible for study inclusion if they had histologically proven squamous cell carcinoma of the *cervix uteri*, stages 3 or 4 [defined by the International Federation of Obstetricians and Gynecologists (FIGO) system (11), and were in a good overall condition with Eastern Cooperative Oncology Group (ECOG) performance status 0-2. Initial staging was based on clinical criteria and did not involve (MRI) or equivalent, since this technology was not readily available in Abidjan. Exclusion criteria included pregnancy, breastfeeding, known Artenimol-R hypersensitivity, history of hearing or balance problems, receiving chemotherapy or radiotherapy, weight <50 kg or >100 kg, and concomitant medication interacting with Artenimol-R. All patients included in the study gave their written, informed consent presented in the local common language of the region. The protocol was reviewed and approved by the independent Ethics Committee, 'Le Comité National d'Ethique des Sciences de la Vie et de la Santé (CNESVS)' of Ivory Coast.

Treatment. In order to prevent tumor lysis phenomena, it was decided that dosing and increased dosage would be carried out with care. Dosing of artenimol-R started at 100 mg/day (two tablets of 50 mg) during the first week. If no adverse event qualifying as National Cancer Institute (NCI) grade III or IV occurred during the first week, the dose was increased to 200 mg/day (1 tablet of 200 mg) as a single dose administration for the subsequent three weeks. Artenimol-R used in this study is the succinate ester of Artenimol. The tablets (50 mg and 200 mg) for oral administration are manufactured under licence according to Good Manufacturing Practice by Dafra Pharma Ltd (Turnhout, Belgium). Quality control of the medication is assured by Dafra Pharma Ltd in accordance with the appropriate regulatory framework. Study medication was imported, stored and dispensed by the principal investigator according to the instructions of the manufacturers.

Clinical symptoms. The clinical symptoms, vaginal discharge and pain were followed up daily for the 28-day treatment period. In the follow-up period, the time until clinical relapse (defined as re-occurrence of vaginal pain and discharge) was recorded.

Safety. Toxicities were graded using the NCI Common Toxicity Criteria CTCAEv3.0. Laboratory assessments were made at the beginning of the study and on day 7, 14 and 28; particular regard was given to evidence of bone marrow toxicity, with hematological assessments also graded according to the NCI CTCAE system.

Immunohistochemical analysis. Immunohistochemistry is used for gynecological tumor characterization, in order to provide additional information critical to the optimal clinical management of the patients (12). Tissue was collected at the onset of the study for confirmation of diagnosis (time point 1) and after 14 days (time point 2) and 28 days (time point 3) of treatment with Artenimol-R. Sections (4 μm-thick) were cut from formalin-fixed, paraffin-embedded tissue and mounted on Superfrost® Plus microscope slides (Thermo Scientific, Braunschweig, Germany). The slides were deparaffinized, rehydrated and placed in a pre-warmed staining dish containing the Retriever with EDTA. The dish was then put in a steamer, covered and steamed for 20 minutes. The slides were then cooled on ice for 10 min. After two washing steps in washing buffer (Thermo Scientific) immunohistochemical staining of (CD71), (EGFR) (1:50), Ki-67 (1:100), CD31 (1:50), or p53 (1:200;

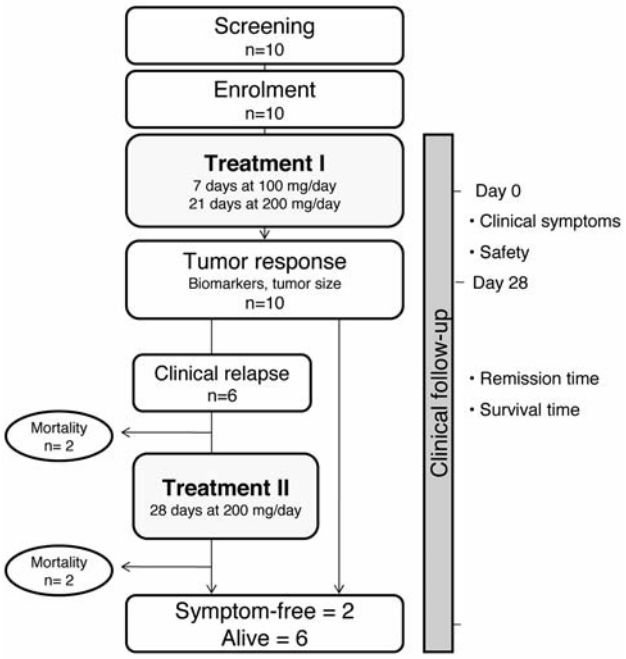

Figure 1. *Study design and follow-up phase. Clinical symptoms in terms of pain and vaginal discharge, and safety were followed up during the first 28 days of the study. A tumor biopsy sample and computed tomographic scan were taken at day 14 and 28 of the study. After the initial treatment period, patients were followed up and the relapse of symptoms was recorded. The time to relapse was calculated from the end of the first administration of Artenimol-R as a reference point. The reference for the survival was the start of the treatment.*

DAKO, Denmark) was performed in a humid chamber according to the instructions provided by the manufacturer. The slides were incubated for 20 min with the primary antibody and processed using the Ultravision Quanto Detection System (Thermo Scientific) with diaminobenzidine (DAB) as chromogen and covered. The percentage of positive stained cells for all slides was calculated for three microscopic fields (× 200) using a computer-assisted semi-quantitative cell counting system (Image J cell-counter; http://rsbweb.nih.gov/ij/plugins/Cell-counter.html).

Results

Patient characteristics. The study was conducted in Abidjan, Ivory Coast, between August 2008 and August 2010, and was designed to include ten patients who fulfilled inclusion and exclusion criteria. An overview of the study design is given in Figure 1. Patients were aged between 39 and 70 years old. Other relevant clinical characteristics at admission are summarized in Table I. A grade 4 hemoglobin (Hb) concentration was found in one patient (005), with a hemoglobin concentration of 5.7 g/dl on the screening day of the study. Grade 3 hemoglobin abnormality was also found in two patients (001, 003), with haemoglobin values between 6.5 and 8 g/dl on screening. One patient was diagnosed with stage 3A disease (patient 006) and four patients (002, 003, 005, 010) with stage 3B, as defined by tumor spreading into the pelvic sidewall, hydronephrosis, or non-functioning kidney. Five other patients had cervical cancer in stage 4, four in stage 4A (001, 004, 007, 008) and one in stage 4B (009) with carcinoma extending beyond the true pelvis with involvement of the mucosa of the bladder and/or rectum.

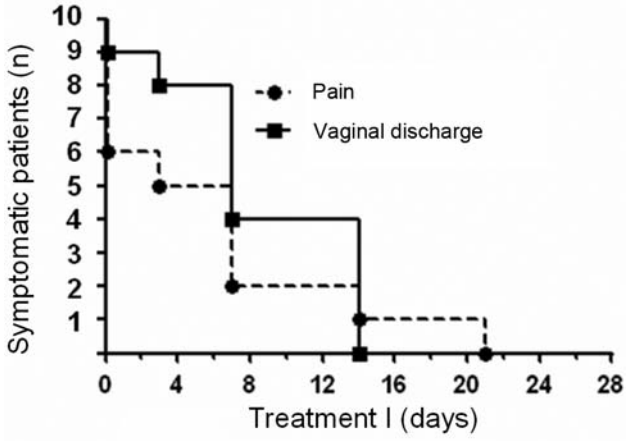

Figure 2. *Pain and vaginal discharge symptoms during the 28-day treatment period for nine patients. At screening, one patient did not experience pain and four patients did not have vaginal discharge.*

Clinical symptoms. According to the protocol, the dose of artenimol-R was increased to 200 mg/day as a single dose for three weeks of treatment after one week at the dose of 100 mg/day. Following the initial treatment period, all patients were monitored for clinical symptoms, pain and vaginal discharge (Figure 1). Clinical symptoms were followed up daily during the 28 day treatment period. As shown in Figure 2, at the end of the first treatment period, disease in all nine symptomatic patients was in a state of clinical remission. The median time for disappearance of pain and vaginal discharge was 7 days (range 3 to 21 days).

Safety. No adverse event qualifying as NCI CTCAE grade 3 (severe) or 4 (life-threatening or disabling) occurred during the first four weeks of treatment in any of the ten patients. Five of the patients treated did not experience any adverse event during the entire first treatment period. The adverse events occurring in the other five patients were grade 1 or 2 and described as transient 'flu-like syndrome', headache and abdominal pain. No abnormal leukocyte counts (qualified as below $3x10^3/mm^3$) were measured during the first 28-day treatment period.

Tumor markers. To obtain a possible signature of the effect of artenimol-R at the molecular level, biomarkers of tumor growth and cell proliferation were immunostained in fixed biopsy samples of three patients before (time point 1), during (day 14, time point 2) and after the 28-day treatment (time point 3).

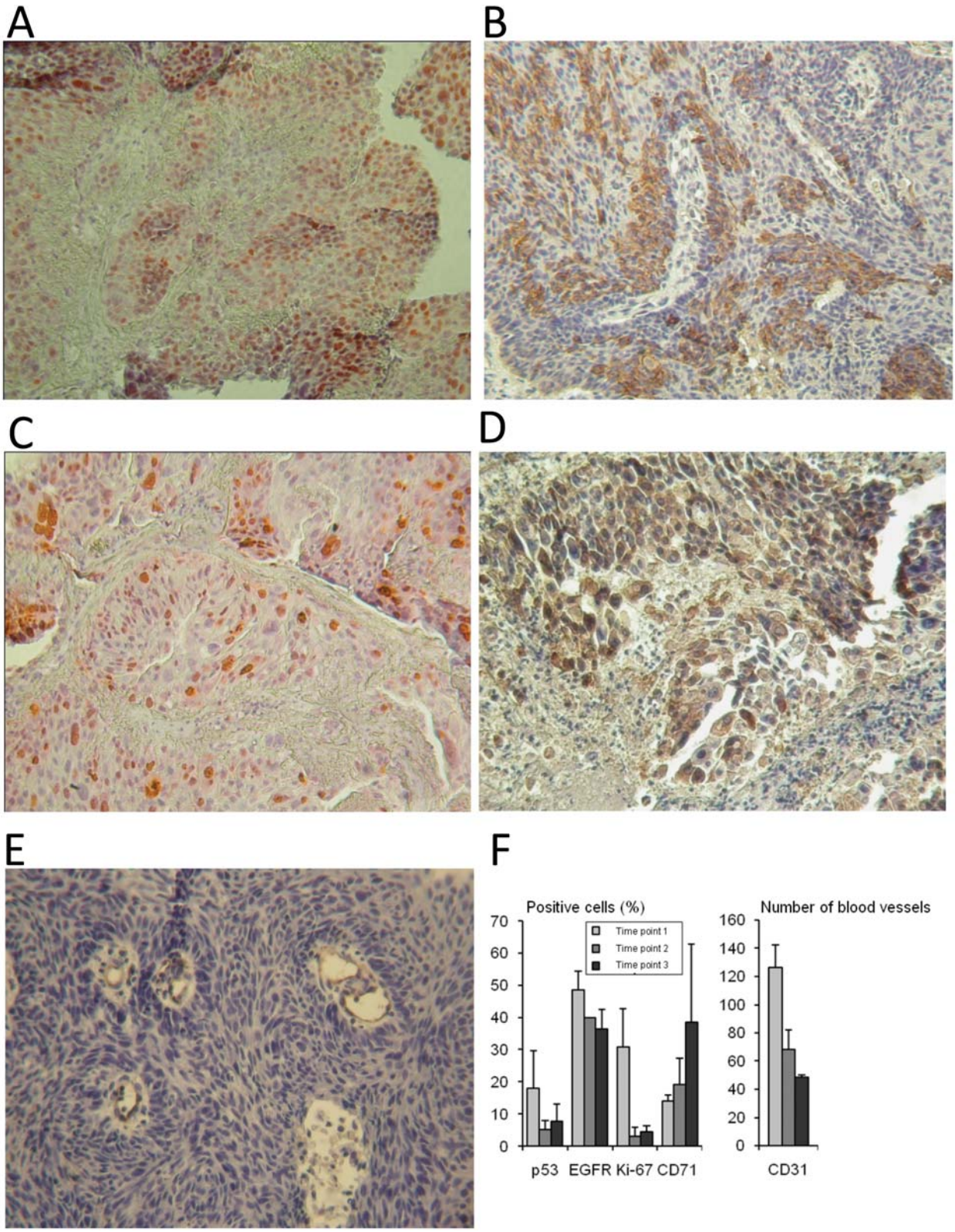

Figure 3. *Selected images of immunohistochemistry for biomarkers p53 (A), EGFR (B), Ki-67 (C), CD71 (D) and CD31 (E) in biopsies from three cervical carcinoma patients. Magnification is ×250. F: Quantification of the immunohistochemical analysis of biomarkers p53, EGFR, Ki-67, CD71 and CD31 before treatment (time point 1), after 14 days (time point 2) and 28 days treatment (time point 3). Mean and SEM (standard error of the mean) are represented.*

Based on previous work, the following markers were selected: tumor suppressor protein p53, epidermal growth factor receptor (EGFR), Ki-67 antigen, transferrin receptor (TFRC, CD71) and the von Willebrand factor (CD31) (13-15). Representative images of immunohistochemically stained uterine cervix biopsies samples are shown in Figure 2 A-E, and the quantitative expression of the selected markers is reported in Figure 2F. The results show a clear down-regulation of p53, EGFR, Ki-67 and CD31, while the expression of CD71 was increased in the biopsy samples (Figure 3). Computed tomographic-scans at the end of the first 28-day treatment period did not show any noticeable macroscopic change in tumor sizes (data not shown).

Follow up period: Clinical remission and survival. The time to relapse was calculated from the end of the first administration of artenimol-R as a reference point (Figure 1; Table I). Five months following the first treatment period, the condition of patient 002 improved sufficiently to allow the removal of the primary tumor by complete hysterectomy. Six patients experienced clinical relapse at an average of 6 months (range 4 to 8 months). Patient 003 and 006 died after 6 and 7 months remission, respectively, before the start of a second treatment period.

Four patients with relapse (001, 004, 005, 007) were challenged with a second 28-day treatment period, which resulted in clinical remission. Patients 001 and 007 subsequently died, 12 and 13 months, respectively, following their initial 28-day treatment. Both of these patients died of renal insufficiency. The two other patients who received the second treatment schedule (004 and 005) as well as four patients who had not yet experienced relapse after the first treatment period are in remission as of August 2010 (median time of 9 months, range 2 to 24 months from initial 28-day treatment) (Table I). The usual prognosis of patients diagnosed with metastasized cervical carcinoma at the Cancer Services, University Hospital, Treichville, is a survival time of about 4 months. This figure is also quoted by gynecological centres in Kigali, Rwanda and Nairobi, Kenya. In this context, it is remarkable that the median survival time of the four patients who died during our study was 12 months (range 8 to 13 months) (Table I).

Discussion

Artenimol-R is a novel small lipophilic molecule of plant origin with a unique stereochemical structure, belonging to the class of alkylating trioxanes naturally forced into a pentoxane multiple ring structure with a peroxide function (16). This molecule has been shown to display high cytotoxicity against all human tumor cell lines of the Developmental Therapeutics Program of the National Cancer Institute (USA) (17). Cytotoxicity was also established in radiation- and chemo-resistant cancer cell lines (18). In xenografted animals, artenimol-R reduced both tumor size and tumor vascularization (19). Apart from being a free radical-based broad-spectrum alkylating agent, the compound has pronounced antiangiogenesis properties (20, 21). The antiangiogenesis properties of artenimol-R and derivatives were demonstrated in the chorioallantoic membrane (CAM) assay and the zebra fish embryo model (22). Artenimol-R has been shown to be the first small molecule to display its antiangiogenic effects on both arterial venous and lymphatic vessels (22). The multi-faceted nature of the action of artenimol-R includes protein and DNA alkylation, induction of apoptosis, angiogenesis inhibition, induction of oxidative stress and cell cycle regulation (13, 23-26). Treatment of stage 3-4 carcinoma of the *cervix uteri* is difficult in many African settings and is inadequate because chemotherapy and radiotherapy are often unavailable, with surgery only being recommended for less advanced stages of disease (4). The current study showed for the first time fast clinical improvement in patients after oral artenimol-R administration. The patients of this pilot study were not treated on a continuous basis with artenimol-R since the effects of chronic administration of this drug are not yet documented. The 28-day artenimol-R treatment period induced clinical remission in all patients treated. The median time for the disappearance of vaginal discharge and pain was 7 days. The effect on symptoms of the disease was prolonged after the initial treatment period. The safety profile of the drug during the first treatment period permitted, upon relapse of the symptoms, a re-challenge of the patients for another month. The observed clinical response in this study was associated with the alteration in the expression of relevant tumor proteins. Down-regulation of *p53, EGFR, Ki-67* and *CD31* and up-regulation of *CD71* are established. The down-regulation of (presumably mutated) *p53* and *EGFR* upon artenimol-R treatment may indicate that the malignant features of the tumors were reverted. Down-regulation of Ki-67 clearly indicates that tumor proliferation was slowed down by artenimol-R. The reduction of CD31-stained blood vessels during treatment can be explained by the antiangiogenic activity of artemisinin-type drugs (20, 23). Interestingly, CD71 increased during treatment. Transferrin as source of ferrous iron is known to enhance the cytotoxic activity of artemisinins (14, 27). Whether CD71 up-regulation as treatment contributes to a favourable outcome merits further investigation. Although this preliminary study was only set up to evaluate whether the new therapeutic option, artenimol-R has the potential to positively affect the clinical outcome of carcinoma of the *cervix uteri*, the results are considered to be greatly encouraging and led to the following conclusions: Artenimol-R treatment led to a rapid improvement of the clinical symptoms as defined by vaginal discharge and pain; 28-day treatment of artenimol-R led to clinical remission of about 6 months in all patients treated; artenimol-R allowed survival of patients with advanced-stage disease for about 12 months, despite the absence of other

therapies. The apparent effect of symptom disappearance and prolonged survival warrant larger randomized controlled trials using a prolonged and possibly continuous period of drug administration.

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