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Procedure and clinical assessments of malariotherapy :recent experience in 20 HIV patients

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Objective To demonstrate the side effects of malariotherapy and to explore safe procedures in conduct of malariotherapy for human immunodeficiency virus (HIV) infected patients.

Methods Twenty HIV/ acquired immunodeficiency syndrome (AIDS) patients were selected for the study of malariotherapy and were intravenously infected with Plasmodia vivax to induce therapeutic malaria. Malaria was terminated with chloroquine after 10 – 20 malarial febrile episodes. Clinical assessments were made before (baseline), during (malarial phase) and after (post) termination of malaria. The density of Plasmodia in peripheral blood from the HIV/AIDS patients were compared to that from HIV-negative naturally infected malarial patients who donated the blood for the therapeutically induced malaria. CD_4 cell baseline levels were correlated to the severity of malarial symptoms and parasitemia.

Results There were no significant differences of Plasmodium density between the HIV/AIDS patients injected with P. vivax and the HIV-negative blood donors. However, it was found that the HIV-positive patients had milder malarial symptoms and parasitemia with progressively lower CD_4 cell baseline levels. All patients developed every day or every other day fever episodes with headache and shaking chill. These symptoms were well tolerated with the aid of anti-pyretic medications. Spleen and liver enlargement were seen in 15 of 20 and 4 of 20 patients respectively. Transitory liver effects with increase of serum glutamic-pyruvic transaminase were seen in 2 of 20 during malarial phase. Most patients experienced mild to medium anemia and 6 of 20 patients developed thrombocytopenia during malarial phase. All these side effects disappeared after termination of malaria or within one month thereafter. No complications occurred in these patients.

Conclusions Therapeutically induced acute vivax malaria was well tolerated in 20 HIV-positive subjects who represented a range of CD_4 cell levels from 1868/μl to 15/μl. Malariotherapy did not induce complications while increasing CD_4 cell levels in most treated HIV/AIDS patients (results published elsewhere).

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In medical history, successful examples of using one disease to prevent or treat another included the applications of cowpox for prevention of smallpox[1,2] and malariotherapy (therapeutic malaria) for treatment of neurosyphilis.[3] This concept has been expanded in our recent studies[4,5] of malariotherapy for treatment of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS). In these preliminary studies, malariotherapy induced high level activities of interleukin-2 and interferon-γ, followed by increases of CD_4 cell levels and decreases of percentages of CD_4 cell apoptosis in most treated HIV infected patients.

The aim of malariotherapy is to reverse abnormality of the

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immune system caused by HIV infection and restore immune function needed to contain HIV infection. Another advantage of malariotherapy is that only a very short term treatment (10 malarial fever episodes, that is, a duration of 10 – 20 days) is given. Side effects subsequently are transient and mild if well controlled. Moreover, malariotherapy may be especially suitable for the treatment of HIV/AIDS patients living in developing countries (accounting for about 95% of world total) as the cost is minimal while its efficacy is confirmed.

Malariotherapy, widely used in treating neurosyphilis in European countries and the United States, however, has not been practiced for about 30 years.[3] Today, malaria is not epidemic in developed countries; furthermore, over the past three decades developed countries have not addressed malaria or malariotherapy in their medical training. Indeed, many physicians are apprehensive that induced malaria is going to cause discomfort or complications. Because of these reasons, this paper presents the procedures and clinical assessments as well as our clinical experience with malariotherapy in HIV/AIDS patients.

Review board discussions on this proposal were organized respectively by the Municipal Department of Health of Guangzhou, by the Provincial Department of Health of Guangdong and by the Provincial Committee of Science and Technology of Guangdong, China. A final approval of phase-Ⅰ – Ⅱ studies of malariotherapy for HIV/AIDS was obtained from these three levels of review boards.

METHODS

Twenty HIV/AIDS patients (all were HIV-1 positive by ELISA testing and confirmed by Western blot), who were naive of any kinds of antiretroviral therapy at entry, were selected for the phase-Ⅰ – Ⅱ studies of malariotherapy. Informed consent was obtained from all patients before the treatment. CD_4 cell baselines were measured by APAAP[4,5] method, a solid-phase immune enzyme assay in cases 1 – 8 and by flow cytometry in cases 9 – 20. Before the therapy in cases 1 and 3 – 13 CD_4 cell levels were ≥500/μl; cases 2 and 14 – 18 were 499 – 200/μl and cases 19 and 20 were <200/μl (Table 1). The clinical data baselines of the patients are listed in Table 2. Ages of the patients were 21 – 42 years old at entry. Cases 17 and 20 are women, the others are men. Cases 1, 2, 13, 19 and 20 contracted HIV from sexual transmission, the others from injecting drug use (sharing needles). Cases 3 – 8 came from malarial endemic areas and the others lived in non-endemic regions. Case 20 was a patient in the very late stage of AIDS accompanied by ulcers of external genitalia, pneumocystis carinii pneumonia (PCP, clinical diagnosis) with dyspnea, needed oxygen inhalation and Karnofsky's score of only 10 – 20 before malariotherapy. There were no other symptoms but enlargement of lymph nodes in case 1 and no other HIV-related symptoms, but enlargement of lymph nodes (Table 2) in cases 2 – 19 (case 19 was classified as an AIDS patient according to the 1993 AIDS definition of Centers for Disease Control and Prevention of USA).

Table 1. CD_4 T-cell baseline levels of HIV/AIDS patients pre – malariotherapy

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	889	269	1610	730	1868	1056	924	705	1217	1043	688	663	590	348	290	260	234	208	144	15

Therapeutic malaria was induced according to our research protocol.[4,5] Clinical assessments included patients' constitutions, symptoms and signs of malaria and related laboratory tests before (baseline), during (malarial phase [assessments were given at least 2 times per week at this phase]) and after (post) malaria. Plasmodium density of peripheral blood from HIV/AIDS patients was compared with that from parasitized blood donors (the mean value of parasite density during the 4th through the 7th fever episodes in the HIV/AIDS patients was compared with that of the blood donors because all malarial blood was taken from the donors during the 4th through the 7th malarial fever episodes). CD_4 cell baseline levels were correlated to the severity of malarial symptoms (represented by fever severity) and parasitemia.

RESULTS

Clinical incubation periods (from injection of Plasmodium to beginning of malarial fever) were 5 – 17 days. All the patients got febrile paroxysm every day or every other day with confirmed malarial parasitemia. Chloroquine was used to terminate malaria after 10 – 20 fever episodes (10 – 20 episodes in cases 1 – 7 and exactly 10 episodes in cases 9 – 11 and cases 13 – 19). Malarial fever and parasitemia naturally disappeared in case 12 (5 episodes) and case 20 (2 episodes) without using any anti-malarial drug. Malarial fever in case 8 (5 episodes) also naturally disappeared but parasitemia still existed and needed chloroquine for termination of parasitemia. All patients were cured of malaria without recrudescence or relapse after one standard course of chloroquine

Table 2. Clinical data of HIV/AIDS patients who received malariotherapy (n = 20)

Clinical parameters	Baseline		Malarial phase		Post-malaria	
	Range/(–)/N#	Mean/(+)/Ab*	Range/(–)/N	Mean/(+)/Ab	Range/(–)/N	Mean/(+)/Ab
Karnofsky[a]	20 – 100	96. 0	60 – 90	68. 0	90 – 100	99. 5
Weight (kg)	41 – 62	53	41 – 63	54	43 – 62	54
Blood pressure (systolic/diastolic)[b]	98 – 135/53 – 90	113/68	90 – 120/53 – 75	105/68	98 – 113/60 – 75	105/68
Pulse (per minute)	74 – 96	81	88 – 152	121	76 – 88	80
Temperature (℃)	35. 5 – 37. 8	36. 6	38. 4 – 42. 0	41. 1	36. 2 – 36. 836. 5	
Headache[c]	20/20 (–)			20/20 (+)	20/20 (–)	
Shaking chill[d]	20/20 (–)			20/20 (+)	20/20 (–)	
Sweating[e]	20/20 (–)			20/20 (+)	20/20 (–)	
Lymph node[f]	1/20 (–)	19/20 (+)	2/20 (–)	18/20 (+)	2/20 (–)	18/20 (+)
Spleen[g]	20/20 (–)		5/20 (–)	15/20 (+)	16/20 (–)	4/20 (+)
Liver[h]	20/20 (–)		16/20 (–)	4/20 (+)	20/20 (–)	
Musculoskeletal[i]	20/20 N		20/20 N		20/20 N	
Neurological[j]	20/20 N		20/20 N		20/20 N	
Psychological[k]	20/20 N		20/20 N		20/20 N	
Vision evaluation[l]	20/20 N		20/20 N		20/20 N	
Chest-X-ray	19/20 N	1/20Ab[m]	19/20 N	1/20Ab[m]	19/20 N	1/20Ab[m]
EKG	19/20 N	1/20 Ab[n]	19/20 N	1/20Ab[n]	19/20 N	1/20Ab[n]
Stool[o]	20/20 N		20/20 N		20/20 N	
Urinalysis[o]	20/20 N		20/20 N		20/20 N	
BUN[p]	20/20 N		20/20 N		20/20 N	
Hemoglobulin[q]	102 – 163	126	65 – 146	110	80 – 139	108
Red blood cell[r]	3. 40 – 4. 80	4. 29	2. 21 – 4. 87	3. 40	2. 46 – 4. 43	3. 62
% Eosinophil	0 – 6	1. 0	0 – 1	0. 1	0 – 1	0. 2
Platelet[s]	80 – 300	162	30 – 210	114	110 – 345	203
White blood cell[t]	2. 1 – 12. 3	6. 6	2. 0 – 6. 9	4. 7	2. 9 – 11. 3	6. 1
% Lymphocyte	23 – 67	39	30 – 57	40	24 – 50	38
SGPT (ALT)[u]	20/20 N		18/20 N	2/20 Ab	20/20 N	
Total bilirubin[v]	20/20 N		20/20 N		20/20 N	

#: N = Normal; *: Ab = Abnormal; a: Karnofsky scores or performance assessments; b: the unit is mmHg; c: no headache is defined as (–), tolerant headache as (+), intolerant (need to terminate malaria) as (++); d: measured as headache; e: no sweating as (–), sweating as (+); f: no enlargement as (–), size like bean to broad bean as (+), apparently larger than broad bean as (++); g: impalpable as (–), palpable within 3 cm under rib costa as (+), over 3 cm under rib costa as (++); h: measured as spleen; i: musculoskeletal evaluations including myodynamia, muscular tension and joint movement; j: including physiological and pathological reflex examination and visual memory test; k: examined by conversation; l: vision evaluated only by visual acuity test chart; m: in case 9, there were flaking and striping shadows in the fields of up lungs, diagnosed lung tuberculosis (active), but remained the same in all these time points; n: in case 5, incomplete right bundle-branch block, no change in these time points; o: including WBC, RBC and occult blood examination; p: normal value <7.0 nmol/L; q: g/L; r: $\times 10^{12}$/L; s&t: $\times 10^{9}$/L; u: normal value <30 unit; v: normal value <20 μmol/L.

treatment (total 10 tablets of chloroquine, the regimen was 4, 4 and 2 tablets q. d. orally on first, second and third day).

The results of clinical assessments at baseline, during malarial phase and at day 10 after termination of malaria (post-malaria) are described in Table 2. Most patients (except case 20) experienced high fever (over 40℃) and all patients had tolerant headaches, shaking chills and sweating during malarial phase. Lymph nodes seemed to decrease in size in all patients who had enlargement at baseline but only one (case 17) reached the cutoff level judged by the standard described in Table 2. Spleen and liver enlargements were seen in 15/20 and 4/20 respectively during malarial phase and 3/20 and 0/20 post malaria as judged by palpation (all recovered to baselines within one month after malariotherapy). Musculoskeletal, neurological, psychological and vision parameters, chronic abnormalities of chest X-ray (case 9) and electrocardiogram (EKG, case 5) were not affected during malarial phase or post malaria. No jaundice occurred in these patients. No changes in stool routine examination or urinalysis and kidney function, represented by blood urea nitrogen (BUN), were observed during the course of malariotherapy.

Most patients (except case 20) experienced mild or medium anemia during malarial phase, but recovered to baselines within one month after the therapy without blood transfusion. Total trend of white blood cell counts

(WBC) decreased during malarial phase compared to that at baseline (paired t test, $P < 0.001$), but most patients were still at normal levels and recovered at post-malaria (compared to baselines, $P > 0.1$). No change in percentages of lymphocytes were observed during the course of malariotherapy. Platelet levels decreased in 6 (cases 1, 3, 9, 10, 16 and 19) of the 20 patients during malarial phase, but no bleeding manifestation was observed during the phase, thus there was no need of platelet or blood transfusion. The platelet levels quickly recovered post-malaria. Liver transitory effects as represented by the increase of serum glutamic-pyruvic transaminase (SGPT or ALT) were observed in 2 (cases 15 and 19) of the 20 patients during malarial phase but also quickly recovered post-malaria.

Karnofsky performance worsened only at malarial fever time in most patients but quickly recovered between febrile episodes and after termination of malaria. Case 20 (full-blown AIDS patient) apparently experienced clinical improvement including: disappearance of ulcer of the external genitalia, dyspnea and PCP (confirmed by chest X-ray) with recovery of Karnofsky performance (to around normal level) and normal activities after two medium malarial fever episodes. If increase or decrease of body weight by 2 kilograms was judged as gaining or losing weight, 3 (cases 4, 6 and 7) lost and 2 (cases 3 and 13) gained weight among the 20 patients during the malarial phase compared with the baselines; however, 8 (cases 3, 5, 6, 7, 10, 13, 17 and 20) gained and 3 (cases 4, 14 and 19) lost weight among the patients at post-malaria compared with the baselines.

CD_4 cell baseline levels were correlated with clinical manifestations of malarial infection. The fever severity represented by Tsq ("Temperature squares" refers to the mean area represented by the numbers of small squares of all fever episodes on a standardized graph that are enclosed within the temperature curve above the line at 37℃ in a temperature chart, and reflects the height and duration of fever which is one of the major symptoms of malaria) positively correlated to the level of CD_4 cell counts among the HIV/AIDS patients with CD_4 baselines below 500/μl (only those whose CD_4 levels were measured by flow cytometry are involved in the correlation analysis: $r = 0.819$, $P < 0.05$). There was no significant difference ($P > 0.2$) of Plasmodium density between the HIV/AIDS patients [mean ± SD: $(2.0 \pm 1.9) \times 10^3$/μl, total 12 patients namely cases 9 – 20 had Plasmodium calculation] and the parasitized blood donors [mean ± SD: $(2.0 \pm 2.6) \times 10^3$/μl, total 12 HIV-negative blood donors with acute vivax malaria]. Similarly, the density of malarial parasites positively correlated to the level of CD_4 counts among the HIV/AIDS patients with CD_4 baselines below 600/μl ($r = 0.807$, $P < 0.02$). There was no need to terminate malaria before the end of the expected course of the therapy in any patient.

DISCUSSION

It might be expected that more severe immunodeficiency caused by HIV might be found in patients with the greatest malarial symptoms since CD_4 cells play a major role in protective immunity against malaria (either through TH1 subset in inducing production of cytokines and nitric oxide or through TH2 subset in helping production of anti-malarial antibodies).[6-8] However, the findings of our present study are opposite and identical to the results of animal model studies of HIV-like virus and Plasmodium coinfection.[9,10] A hypothesis was proposed by Imberti et al[11] that HIV infection may induce a selective depletion of T-lymphocyte subpopulations that are not involved in the anti-malarial immune response. This seemed to be confirmed by the results of Migot et al[12] that immune response obtained after stimulation of peripheral blood mononuclear cells (PBMC) by Plasmodium schizont extract was not affected in AIDS patients compared with healthy subjects. However, the response to non-specific mitogens such as phytohemagglutinin (PHA) and purified protein derivative (PPD) of tuberculin was apparently damaged in the AIDS patient group. Other researchers also observed in animal models that while development of murine AIDS affected T-lymphocyte memory of infection of malarial parasites, it did not alter Plasmodium killing by macrophages.[9] This may be explained by the hypothesis proposed by Stevenson et al[13] that the parasite is able to induce IL-12 secretion directly by macrophage and then IL-12 induces production of IFN-γ from T and NK cells,[14,15] which will, in turn, maintain macrophage activation. Another, more closely related explanation is the findings by Eckwalanga et al[10] in animal models that infection of HIV-like viruses prevents death from cerebral malaria and the protection induced by murine AIDS increases with the severity of immunodeficiency and IL-10 secreted by splenic T-cells which may play a critical role in protection. However, an additional explanation would be the postulate that there is a mutually inhibitive interaction between these two kinds of pathogens, either through immune responses in the dually infected persons and/or through the components of the pathogens proper.

The symptoms of malaria in these HIV/AIDS patients were not more serious nor more difficult to alleviate than

those in HIV-negative subjects (according to our previous experience in treating over one hundred patients with natural vivax malaria). Side effects such as high fever episodes with headaches and shaking chills, liver enzyme elevation, spleen enlargement, anemia and thrombocytopenia were seen in the course of malariotherapy in HIV/AIDS patients, but they were mild, limited and transient. Most importantly, they were tolerated by the HIV/AIDS patients and accepted by the patients and their physicians as a possible means of achieving clinical and immunological improvement in their HIV/AIDS status. Nevertheless, in doing a clinical trial of malariotherapy for HIV/AIDS, the following criteria must be seriously considered.

Patient selection

According to the results of our phase-Ⅰ-Ⅱ studies of malariotherapy for HIV/AIDS which involved 20 cases, patients with CD_4 count baselines between 200-500/μl are quite suitable for malariotherapy (with or without HIV-related symptoms). Patients with CD_4 baselines over 500/μl appeared not to be suitable for the treatment (the exact mechanism is still unknown). Patients with CD_4 below 200/μl showed transient restoration of CD_4 count and it appears to be helpful in the elimination of opportunistic infections such as PCP and ulcer of genitalia.

In phase-Ⅰ-Ⅱ clinical trials, malariotherapy is not advocated for patients with any of the following conditions: cardiac, renal or liver dysfunction; bronchial asthma, aortic aneurysm, splenomegaly, cachexia, coma or seizures. However, mild to medium glucose-6-phosphate dehydrogenase (G-6-PD) deficiency is not a strict contraindication since there is no need to use primaquine for prevention of malaria relapse (described in the following section). Furthermore, patients with mild or medium neurological impairment or psychological symptoms caused by HIV, including AIDS dementia or neurosyphilis, may be candidates for malariotherapy due to historical success of the therapy for neurosyphilis and on the recent finding that malaria induces IL-1β and IL-6 production[16,17] and these cytokines help the regeneration of neurons[18-20] (this may be a part of the mechanism of malariotherapy for neurosyphilis, which was unknown when the therapy was used in the past).[3] Tuberculosis is also not a strict contra-indication if the patient's general condition is good. In our recent observation, active tuberculosis in an HIV patient was not worsened during and after malariotherapy.

Selection of malarial parasites

Selection of Plasmodia is very important for malariotherapy. According to our experience, selection of hematogenous Plasmodium vivax which is sensitive to chloroquine (this can be judged by treatment with chloroquine for the malarial blood donor) is critical. In Guangdong Province of China, there was a total of over 20 000 patients with natural vivax malaria without death in the past two decades, due in part to the standard chloroquine treatment (in fact, no chloroquine resistant strains of Plasmodium vivax were found in China). Therefore, malariotherapy using hematogenous Plasmodia vivax which is sensitive to chloroquine should be quite safe. Parasitized blood donors must be tested to exclude HIV infection, syphilis, hepatitis A, B, C, D, E, F and G, other kinds of malaria (by repeated thick and thin blood smear examination) and any other infections suggested by history and physical examination. Falciparum malaria must be absolutely excluded since fatality and severe complications caused by the treatment has occurred while using Plasmodia falciparum.[3] Any kind of animal malarial parasites should not be used in malariotherapy (in addition to the known virus inducing yellow fever, many unknown pathogens may exist in animal blood). Mosquito transmitted vivax malaria should not be advocated due to the need for primaquine (used for the prevention of relapse) which may induce intravascular hemolysis (especially in patients with G-6-PD deficiency) and, consequently, renal dysfunction.

In general, safety or "doing no harm" is the most important element in malariotherapy clinical trials. This ethical consideration was repeatedly addressed in numerous review board discussions before approval of the studies on malariotherapy for HIV/AIDS was obtained from the Boards in Guangdong Province, China. In conclusion, our phase-Ⅰ-Ⅱ studies have identified procedures for the safe conduct of malariotherapy for HIV/AIDS. A well controlled phase-Ⅱ-Ⅲ study should be conducted. We do not advocate a routine treatment of malariotherapy for HIV/AIDS without further scientific research and/or without good facilities and well trained staff. Furthermore, HIV-positive patients should not be advised to go to malaria endemic areas to contract natural malaria because this is dangerous without the selection of the form of malarial parasites and without careful medical monitoring.

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