Tokai J Exp Clin Med., Vol. 23, No. 6, pp.427-430, 1999

Docetaxel (Taxotere®): Effectiveness against *Plasmodium falciparum* in vitro and *Plasmodium yoelii nigeriensis* in vivo

Hanns M. SEITZ, F. GOTTWALD, Jana PROFT, F. WINGEN* and W. MAIER

Institute of Medical Parasitology, University of Bonn, Bonn, Germany
**2Rhône-Poulenc Rorer Arzneimittel, Köln, Germany*

Keywords : Docetaxel, *Plasmodium falciparum*, *Plasmodium yoelii nigeriensis*

There is an urgent need for new drugs against malaria parasites, *Plasmodium falciparum* in particular, because the resistance against the actual drugs is still increasing. Even drugs which support or potentiate the compounds now in use would be helpful.

Docetaxel has shown some anti-malarial activities in vitro [2]. The authors showed that the anti-plasmodial effect can be achieved by concentrations of the drug just 0.1% of the anti-tumor level required in tumor therapy. But in vivo experiments showed that only doses are effective against rodent malaria which are toxic for the mice.

Docetaxel is a semi-synthetic product consisting of a baccatin complex extracted from the European yew, *Taxus baccata*, and a synthetic side chain which is bound to the C13. The compound interacts with the subunits of the microtubuli in eukaryotic cells. Docetaxel inhibits the depolymerization and stabilized the microtubuli. In this way the proliferation of cells is inhibited. This cytostatic effect can be used in tumor therapy.

We undertook some orientating experiments to find out if docetaxel really shows promise as a drug in malaria therapy. The drug was tested solely and in combination with established anti-malarial drugs as chloroquine, halofantrine, mefloquine and sulfamethoxazole. We used *P. falciparum* cultures and added various concentrations of the drugs.

First the 50% effective dose (ED_{50}) was determined (Table 1). The values proved to be within acceptable limits.

To give you two examples, the parasitaemia which develops in the culture is shown for the combinations docetaxel and chloroquine (Fig. 1) and docetaxel plus mefloquine (Fig. 2). In both cases there is no difference between the docetaxel containing cultures and the controls, or the cultures with docetaxel show even higher parasitaemia. An additional finding is that the gametocytes of *P. falciparum* develop nor-

Table 1 Material and Methods : Determination of the 50% effective Dose

Drugs	Duration of culture	Concentrations used	Solvents
Docetaxel	24h, 48h, 72h	10^{-7}M - 10^{-11}M	Ethanol
Chloroquin	48h, 72h	10^{-7}M - 10^{-11}M	Aqua dest.
Halofantrin	48h, 72h	$2{,}5 \times 10^{-5}$M - $2{,}5 \times 10^{-9}$M	Ethanol
Mefloquin	48h, 72h	10^{-6}M - 10^{-10}M	DMSO
Pyrimethamin	48h, 72h	10^{-5}M - 10^{-9}M	Lactic acid
Sulfamethoxazol	48h, 72h	10^{-3}M - 10^{-7}M	DMSO

Hanns M. SEITZ, Institute of Medical Parasitology, University of Bonn, Sigmund-Freud-Str. 25, 53105 Bonn, Germany TEL: 49-228-287 5673 FAX: 49-228-287 4330

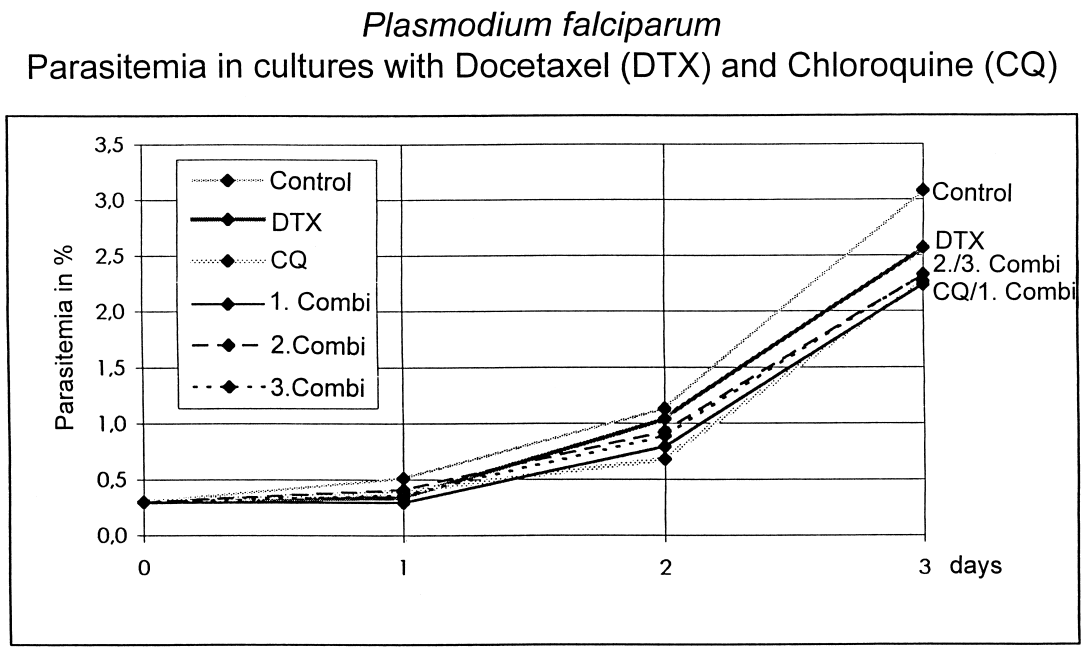

Fig. 1 Development of the parasitaemia in a culture of *Plasmodium falciparum* (NF-54). 1. Combi. = Combination of ED_{50} chloroquine + ED_{50} docetaxel; 2: Combi. = Combination of 20% of the effective dosis; 3. Combi. = Combination of 10% of the effective dosis.

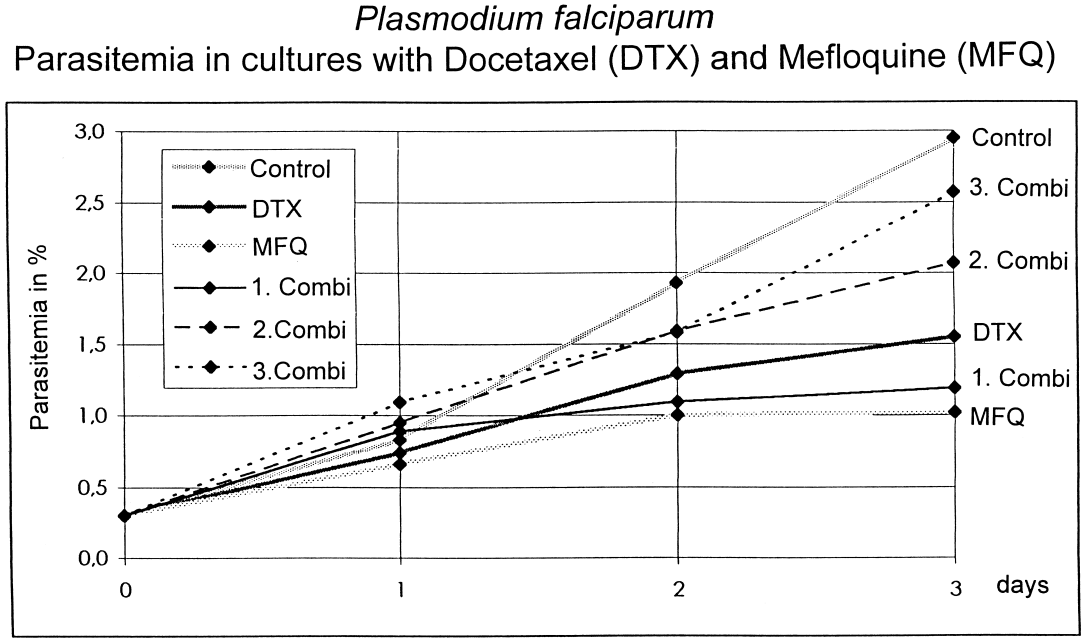

Fig. 2 Development of the parasitaemia in a culture of *Plasmodium falciparum* (NF-54). 1. Combi. = Combination of ED_{50} mefloquine + ED_{50} docetaxel; 2. Combi. = Combination of 20% of the effective dosis; 3. Combi. = Combination of 10% of the effective dosis.

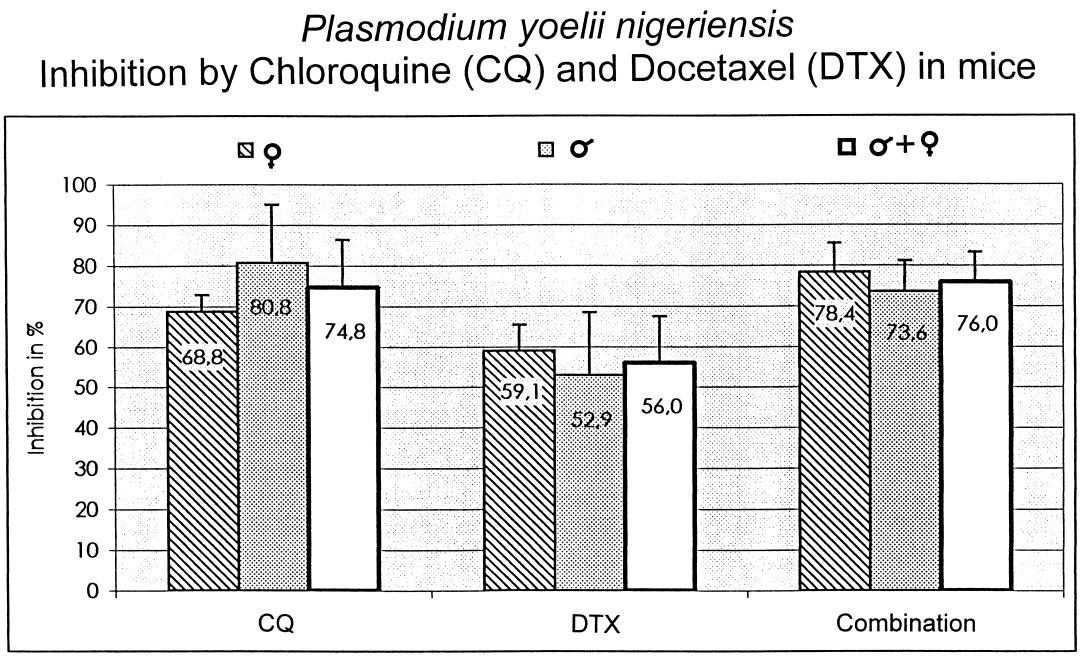

Fig. 3 Inhibition of the parasitaemia in *Plasmodium yoelii nigeriensis*-infected mice by chloroquine (CQ), docetaxel (DTX) and the combination of both. The experiments were carried out according to the 4-days suppression test proposed by Peters [1].

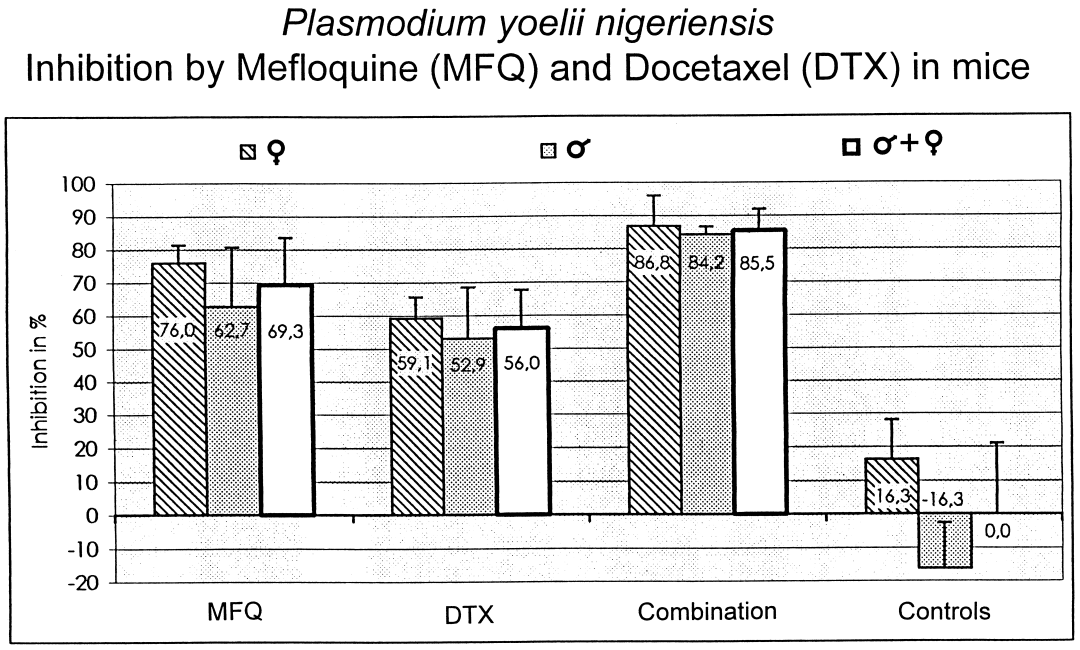

Fig. 4 Inhibition of the parasitaemia in *Plasmodium yoelii nigeriensis*-infected mice by mefloquine (MFQ), docetaxel (DTX) and the combination of both. The experiments were carried out according to the 4-days suppression test proposed by Peters [1].

mally in these cultures, their morphology at least is not affected by docetaxel.

The same drug combinations were used in an in vivo assay, which was the infection of white mice with *P. yoelii nigeriensis*. The results of these experiments showed again that the therapeutic effect of docetaxel by itself or in combination with chloroquine or mefloquine was not significantly better than chloroquine or mefloquine by itself (Fig. 3, 4).

In summary, we do not have any evidence that docetaxel is a compound with a potential as an anti-malarial drug.

REFERENCES

1) Peters W, Richards WHG: Antimalarial drugs I and II. Berlin, Heidelberg, New York, Tokyo, Springer-Verlag, 1984a.
2) Schrével J, Sinou V, Grellier P, Frappier F, Guénard D, Potier P: Interactions between docetaxel (Taxotere®) and *Plasmodium falciparum*-infected eythrocytes. Proc Natl Acad Sci USA 91: 8472-8476, 1994.