

Anticancer drugs for the treatment of malaria: example of methotrexate

Alexis Nzila

Kenyan Medical Research Institute
(KEMRI)-Wellcome Trust Programme



*2nd Stakeholders Meeting
MRC, Cape Town, South Africa
4-7 Oct 2009*

Rational: methotrexate (MTX) for malaria treatment

Using MTX to study folate pathway:

- * **potent against malaria parasite** (including multidrug resistant strains)
- * **IC50 < 50 nM** laboratory strains and field isolates
(Nduati et al. 2008 *Parasitol Res* 102:1227-34, Kiara et al. 2009, *AAC*, 9 (3). P1004).

MTX in human

- * **up to 12g per treatment (320mg/Kg) = in cancer ... very toxic**
- * **low dose (LD-MTX) 7.5-30mg(0.1-0.4) mg/Kg/week /years=**
rheumatoid/juvenile arthritis
 - ** **well tolerated especially in children**
 - ** **30 years of experience of LD-MTX in human (in Africa as well)**
estimated: 1,000,000 patients receive LD-MTX weekly
- * **LD-MTX= MTX concentration high enough to kill malaria**
- * **2.5mg/day/3-5 days = efficacious/safe in malaria (2 old studies, in 1970s).**

Investigate LD-MTX as antimalarial: Phase I



Key findings of Phase I evaluation of MTX

Phase I trial:

- * **dose=** MTX at 5mg/days/5day in healthy adults (45-65 kg)
- * **Follow up=** Admitted for 5 days and follow up to 42.
- * **Parameters to monitor:**
 - ** **Safety:** - Hematology- Clinical biochemistry (liver and Kidney functions)
 - Adverse event: **GI tract disturbance- Nausea, vomiting, oral ulcers**
 - ** **Pharmacokinetics:** blood level of MTX in the body

Results:

- ** **Safety:** - **Hematology:** normal; - **Adverse event:** none of concern
 - **Clinical biochemistry:** increase of ALT enzyme (common in LD-MTX)
 - **1 patient:** was 10 higher (in LD-MTX, pre-existence liver problem)

Data being reviewed by an independent group

** **Pharmacokinetics:**

MTX Cmax=150-300 nM;
after 3H, MTX Ceff < 100 nM yet (IC₉₉= 250 nM)

Conclusion: **5mg/5days: Ceff not high enough..**



Challenges & How Resolved

Target: we want to achieve $C_{max}=500 \text{ nM}$

With 5mg/day/5days (0.1mg/Kg) = C_{max} 150-300 nM

To reach $C_{max}= 500\text{nM}$, we need 10mg-15mg/day/ ($0.2\text{-}0.3\text{mg/Kg}$)
from 5 days to 3 days only..

We want to test 2 doses: 10mg and 15mg/day/3days (0.2mg/kg)

Will it be safe? Yes based on arthritis experience...

in Phase I?

Phase I: healthy volunteers (5mg/kg/5days , already done)

in Phase IIa? in children with malaria (less than 50 each group)
primary endpoint= safety

Conclusion: $10\text{-}15\text{mg/3days}$ ($0.2\text{-}0.3\text{mg/Kg}$) to be evaluated



Future Directions & How ANDI Can Contribute

- **Future plan:**
 - Clinical evaluation of MTX 10-15mg/day/3day**
- **ANDI's Role**
 - Financial support for this evaluation**
- **Other possible work**
 - **to evaluate another anticancer in a Phase I trial:**
 - Trimetrexate**
 - more active than methotrexate
 - better pharmacokinetics
 - **to talk to ANDI about this study as well..**



Acknowledgements

- **KEMRI/Wellcome Trust, Kilifi (financial support of Phase I)**
Prof. Kevin Marsh
Dr Roma Chilengi
Dr Trudie Lang
- **KEMRI-HQ, Nairobi**
Dr Rashid Juma (PI of Phase I)
- **EDCTP (European Union Developing countries Clinical Trials Partnership)**
- **European Union-Antimal grant [with Prof. Steven Ward]**

