

INTEREST OF PHARMACOLOGICAL STUDIES IN THE USE OF IFOSFAMIDE IN CHILDREN

**NICOLE DELEPINE, GERARD DELEPINE,
V. SUBOVICI, S. ALKALLAF, P. ARNAUD,
F. BRION, JC. DESBOIS**

ONCOLOGIC PEDIATRIC SERVICE

SIOP 93

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**STUDIES IN THE
INTERNATIONAL
LITERATURE**

RATIONALE FOR THE STUDY



**Controversies about
effectiveness of Ifosfamide
in children
are not yet resolved**

RATIONALE FOR THE STUDY



- Furthermore, the combination of VAIA is an effective therapy in childhood rhabdomyosarcoma
- A high IFX dosage of 10 gr/sqm per cycle achieved a better response rate (83 %) than a lower dose 6 gr/sqm (68 %) (ASCO 1991)

The German PaediatricOncology Group found :



■ improved response rate in children with Ewing's sarcoma following substitution of IFX for CPX (Jurgens 1989).

RATIONALE FOR THE STUDY

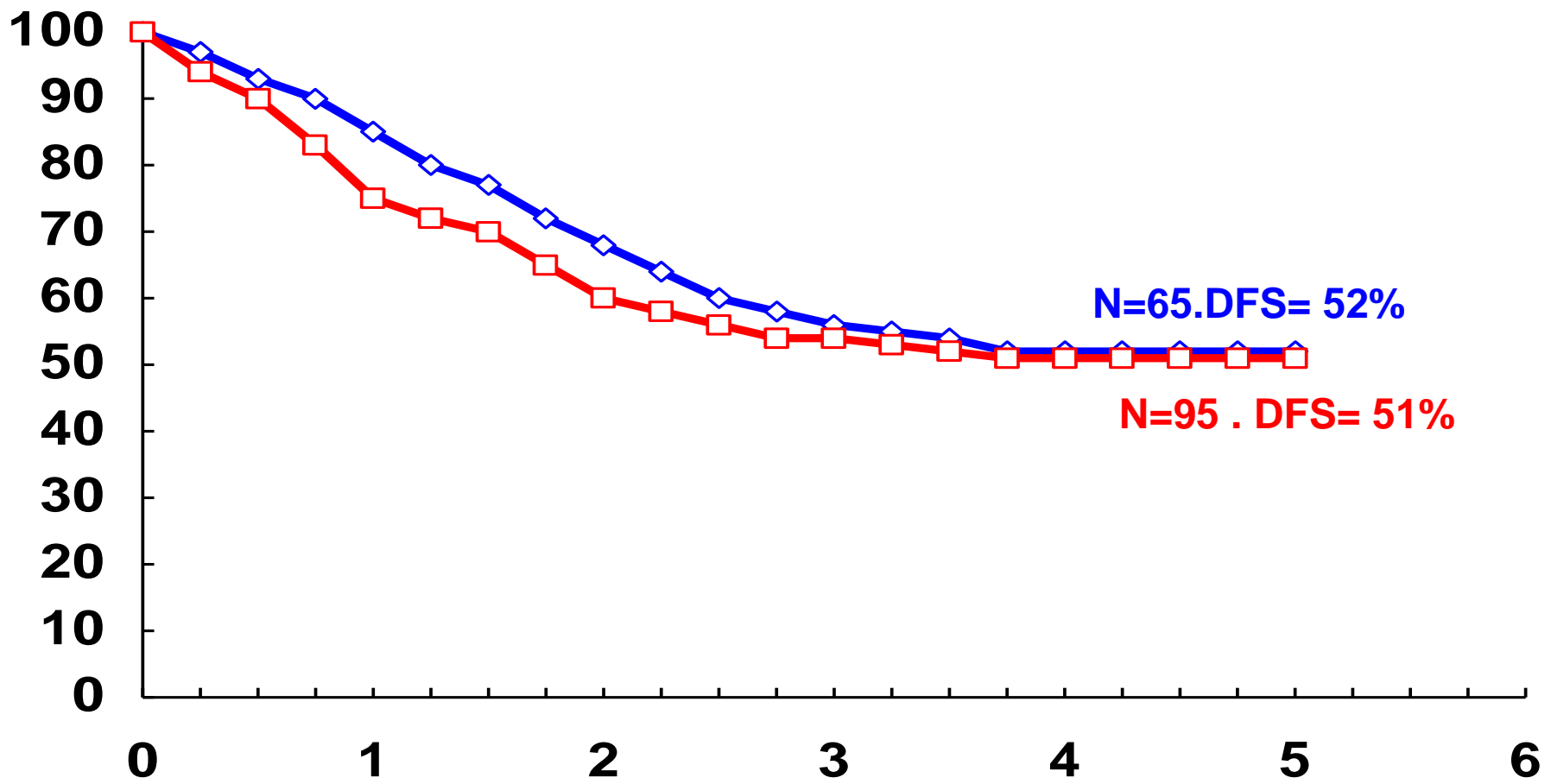


- In contrast, the SFOP IFX based Ewing's sarcoma protocol found:
- no improvement in 3 year survival rate and
- an increased toxicity.

(SFOP - Oberlin and al 1990)

RESULTS OF S.F.O.P. PROTOCOLS VACA AND IVA-

IVAa



RATIONALE FOR THE STUDY



**BACKGROUNDS
OF DISCORDANT RESULTS
COULD BE AGE AND
PHARMACOKINETICS
OF IFX IN CHILDREN**

MATERIAL AND METHODS



- 48 patients aged 1,5 to 25 years with various solid tumors, received 137 courses of IPA (IFX, CDDP, THP ADR) with seric pharmacokinetic study
- IFX was infused thermo-ionic detection
- 1850 dosages were computerized for statistical analysis

PATIENTS :




■ 48 patients

■ 1,5 y to 25 y

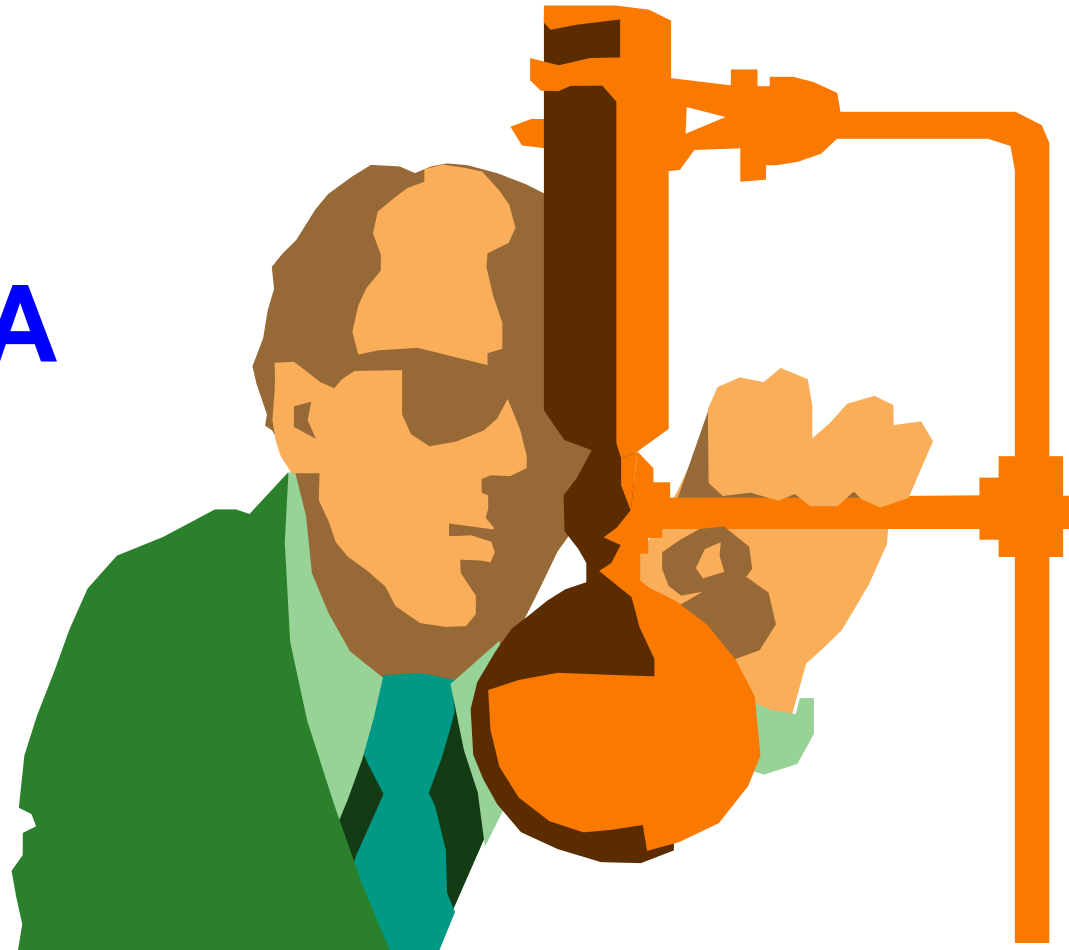
■ Various solid tumors

IFX INFUSION

- 
- **Continuous infusion by pomp 120 hours**
 - **Dosage of IFX by gaz chromatography with thermo-ionic detection.**

METHODS

**1850 SERIC
DOSAGES
WITH GAZOUS
CHROMATOGRA
PHY AND
THERMO IONIC
DETECTION**



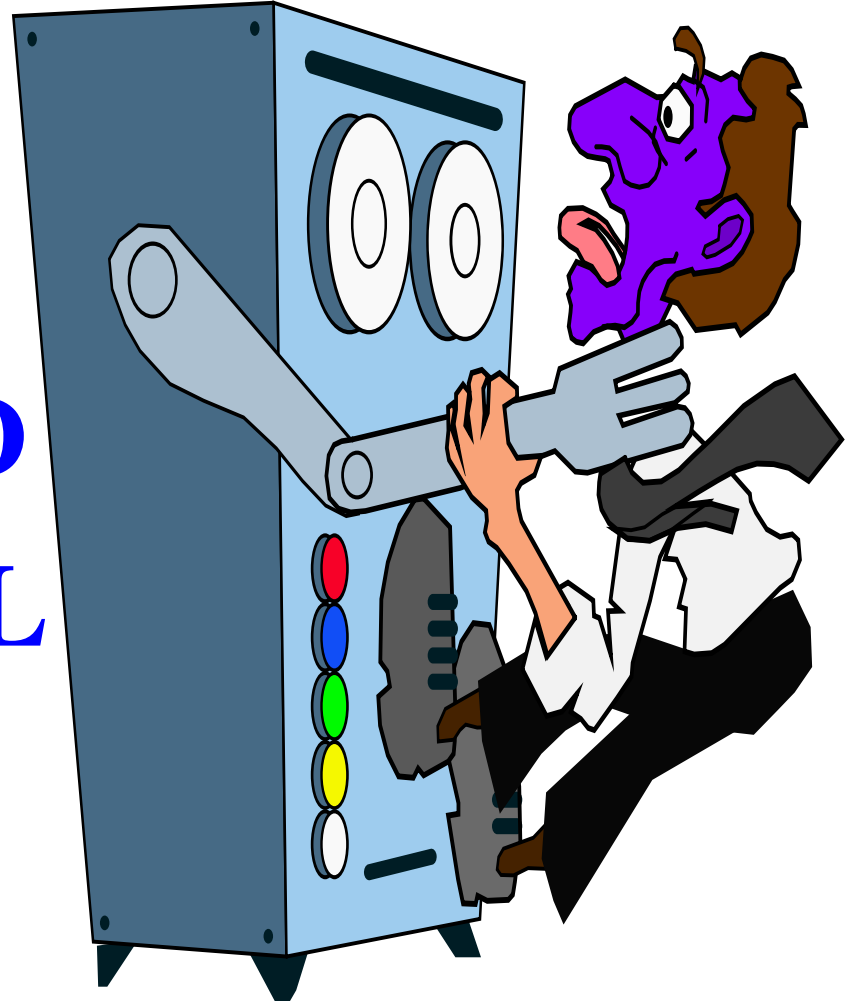
DATAS



METHOD



**1850 DOSAGES
WERE
COMPUTERIZED
FOR STATISTICAL
ANALYSIS**



RESULTS



- **Serum IFX reaches the steady state after 10-12 hours infusion.**
- **Half life increase is 4 hours
(min 2 h 30 - max 7 h)**

RESULTS

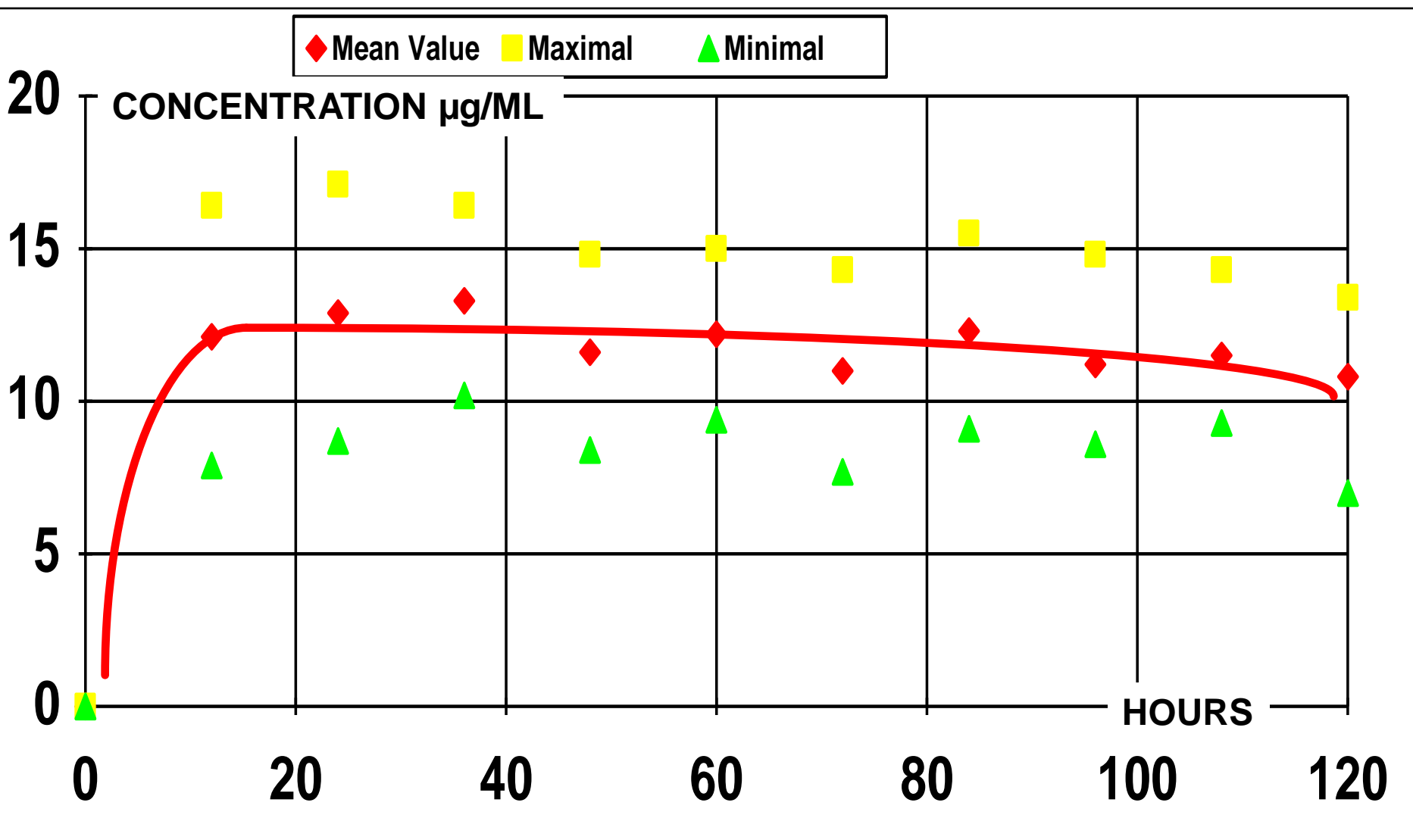


■ A significant difference of mean seric level was found from day 1 to day 5 :

For the daily infusion of 1,2 g/sqm:

- average D1 seric level is $12,63 \cdot 10^{-3}$ g/l
- and average D5 seric level $9,81 \cdot 10^{-3}$ g/l

EVOLUTION OF SERIC CONCENTRATION OF IFX




RESULTS

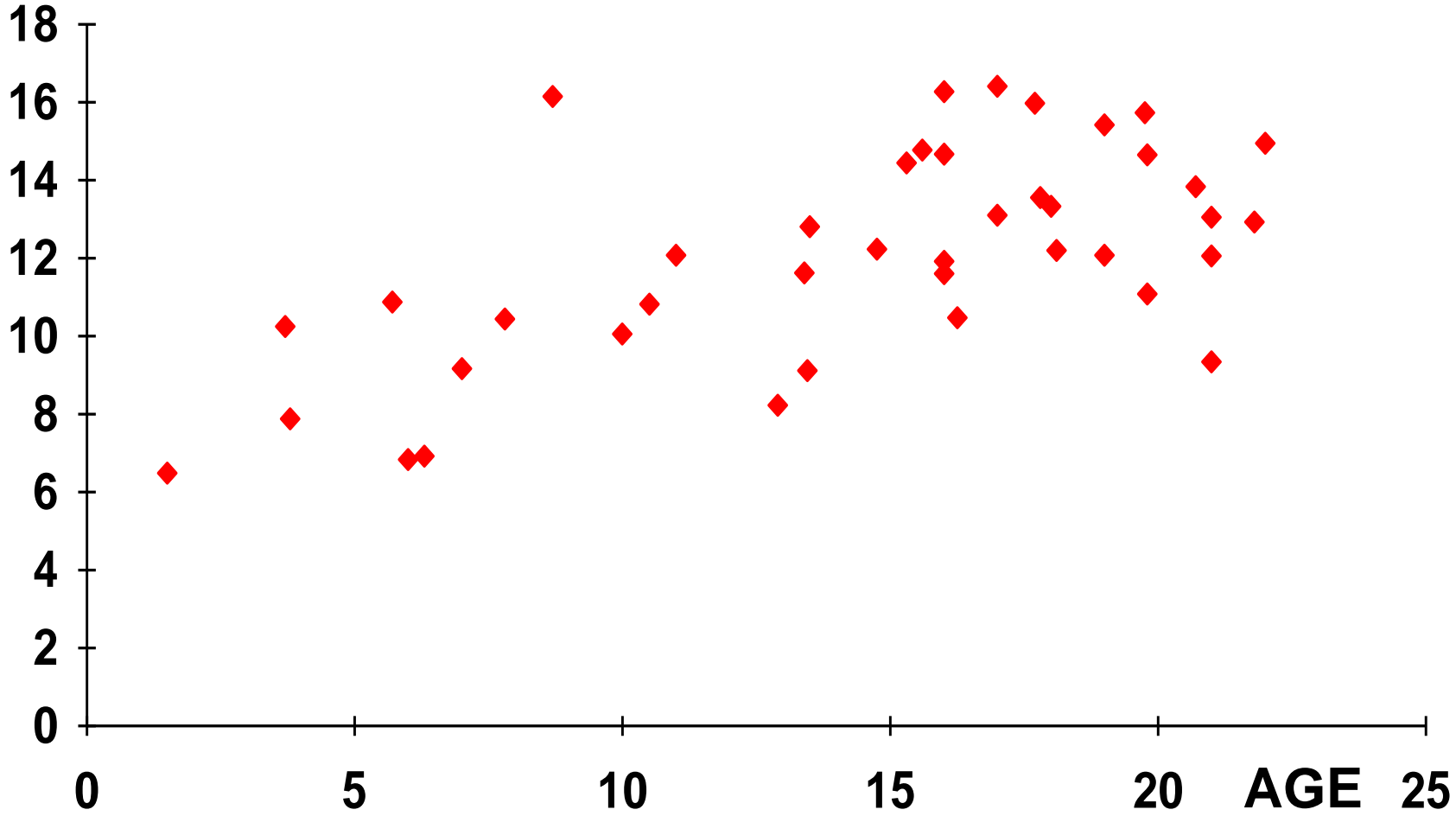


- For a daily infusion of $1,2 \text{ g/m}^2$
- the average seric level is $12,15 \cdot 10^{-3} \text{ g/l}$ (min 6,5 - max 20)
- The average seric IFX clearance is 72 ml/min (min 50, max 120)

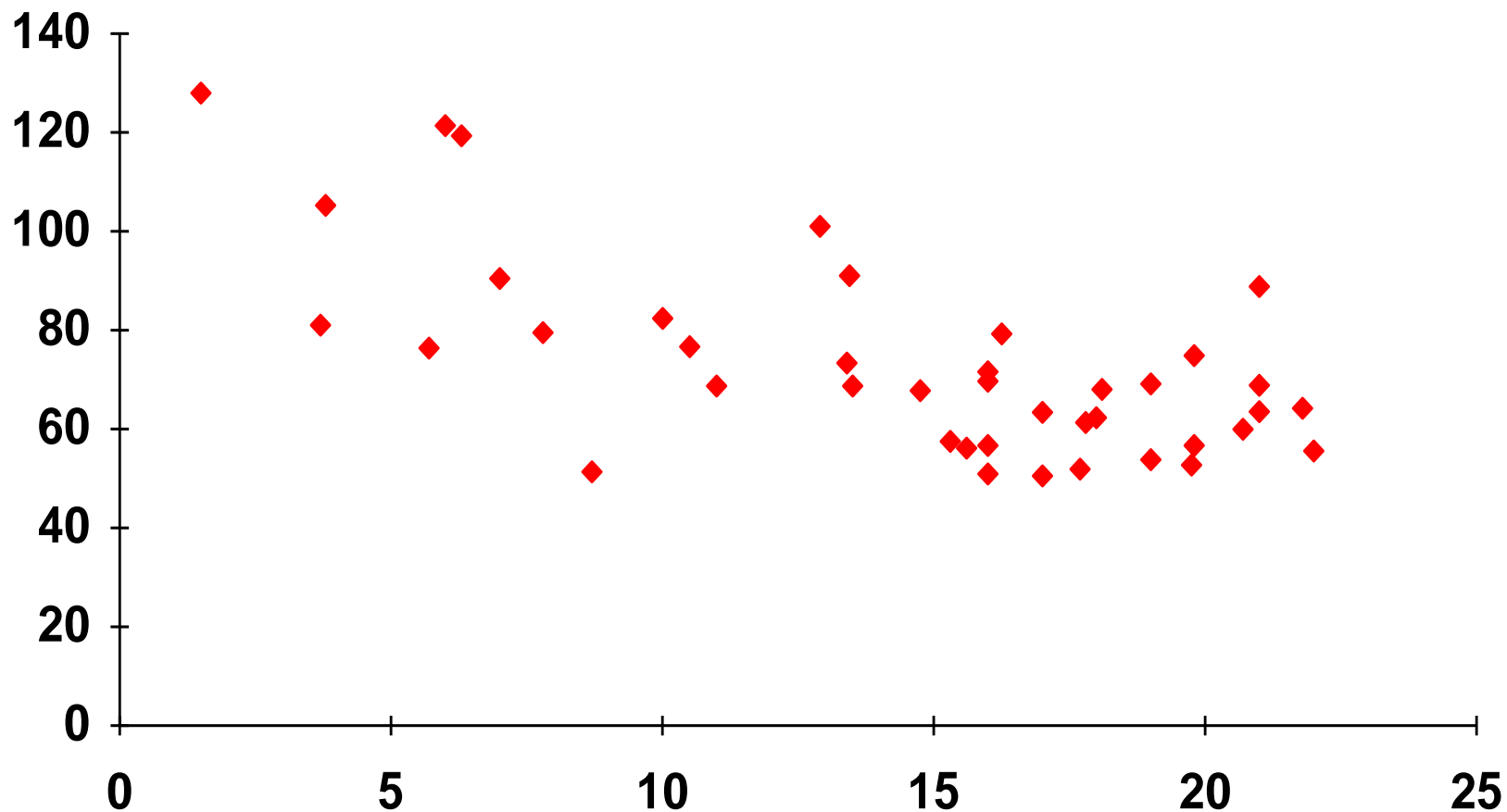
RESULTS

- 
- **The seric clearance is significantly correlated ($p < 0,001$) with age.**
 - **Young patients show a higher clearance and a lower seric concentration for a fixed dosage than older patients.**

CORRELATION ENTRE L' AGE ET LA CONCENTRATION SERIQUE A L'EQUILIBRE.



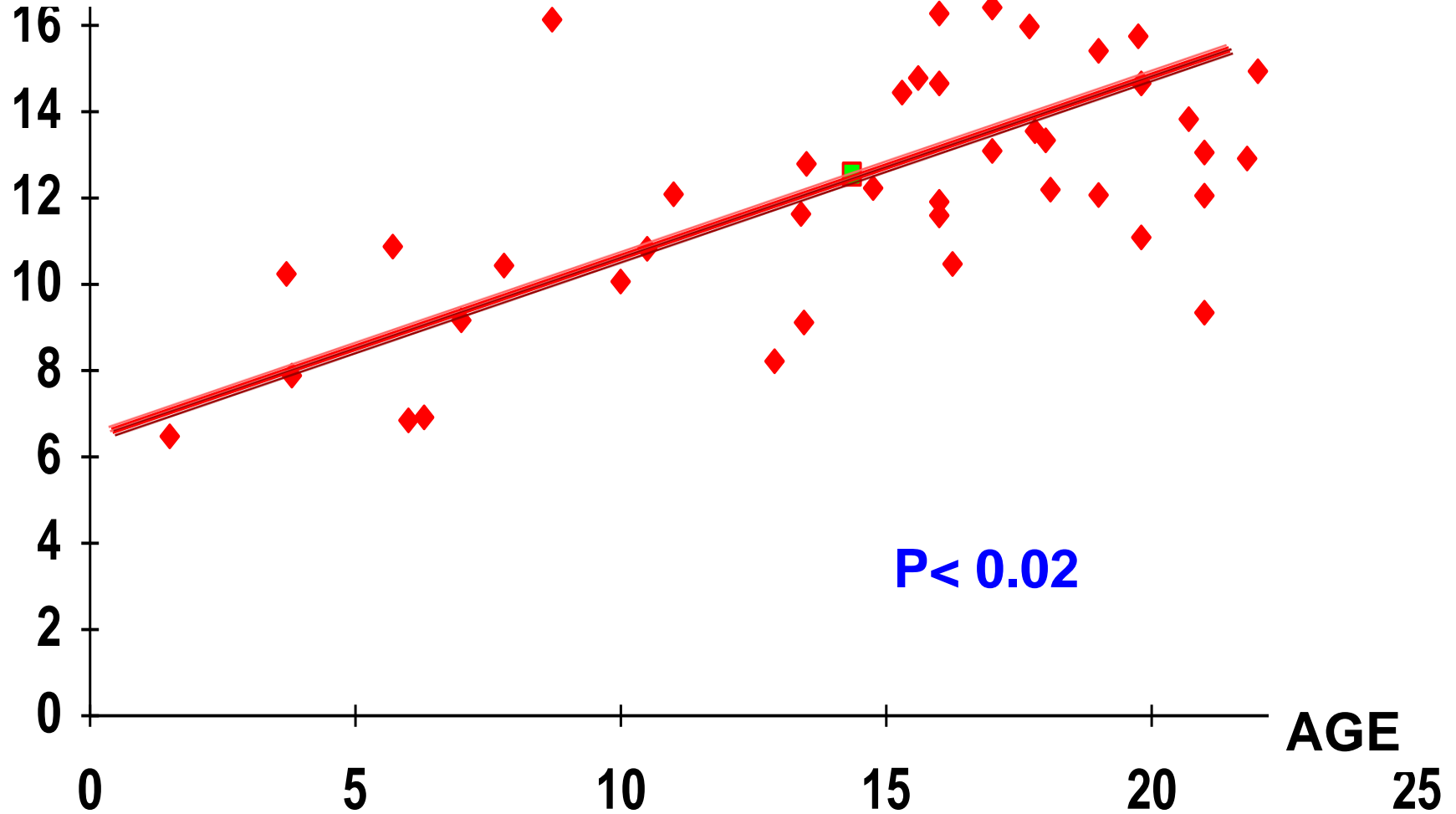
CORRELATION ENTRE L' AGE ET LA CONCENTRATION SERIQUE A L'EQUILIBRE.



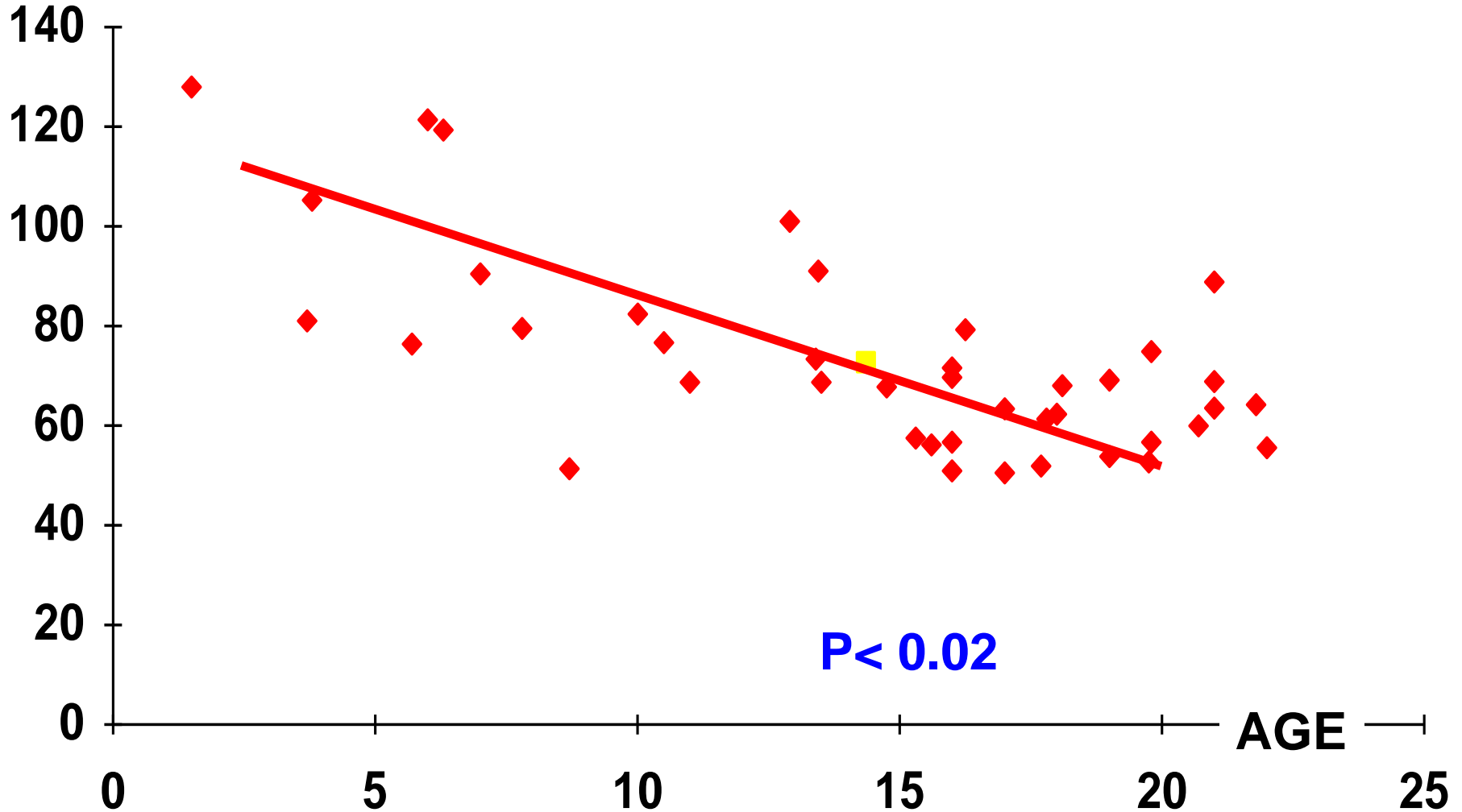
CORRELATION BETWEEN AGE AND SERIC CONCENTRATION .




MEAN SERIC CONCENTRATION




CORRELATION BETWEEN AGE AND SERIC CLEARANCE .



CONCLUSION

- 
- **Significant correlation of IFX clearance with age could explain lower apparent effectiveness in young children at fixed dosage.**
 - **Further studies are needed to find the best C_p plateau concentration or best AUC effective in different pathologies**

CONCLUSION



**Significant correlation
of IFX clearance with age
could explain failures of
effectiveness of IFX
in young children
with a fixed dosage**

CONCLUSION



**Further studies are needed
to find the best plateau
concentration or the best
AUC
effective in different
pathologies**



■ Ability of IFX to produce response in patients with pediatric solid tumors refractory to CPX has been clearly demonstrated

■ Response rate as single agent in patients previously exposed to CPX, 24 to 32 %



■ HIGHEST LEVEL OF RESPONSE IN
TUMORS PREVIOUSLY TREATED
BY CPX :

- EWING
- WILMS
- OSTEOSARCOMA
- RHABDOMYOSARCOMA

■ Magrath 1986 - Pinkerton 1989

■ Pratt 1989 - Schwartzmann 1989