

A pharmacologic analysis
of
perioperative administration of 5-FU
in
patients with peritoneal carcinomatosis

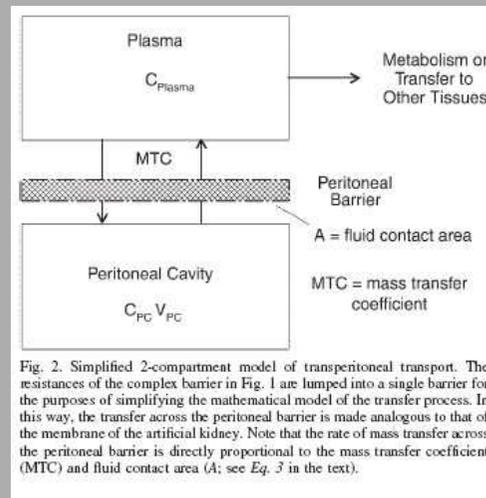
K. Van der Speeten
O. A. Stuart
H. Mahteme
P. Sugarbaker



Introduction

Perioperative chemotherapy: encouraging clinical results in PC patients

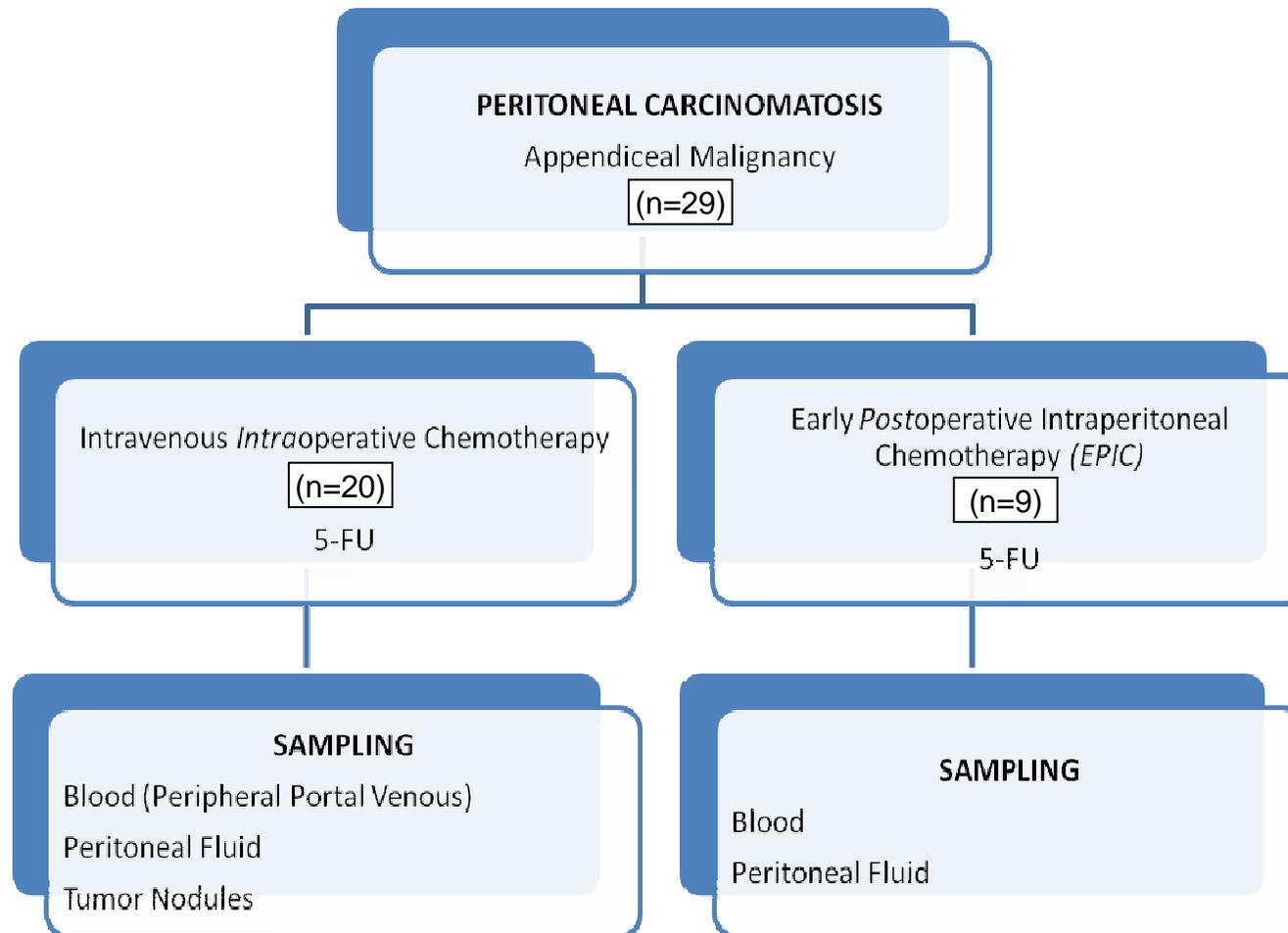
1. IP/IV dose intensification reflects clinical efficacy



2. IP drug to reach high IP concentrations

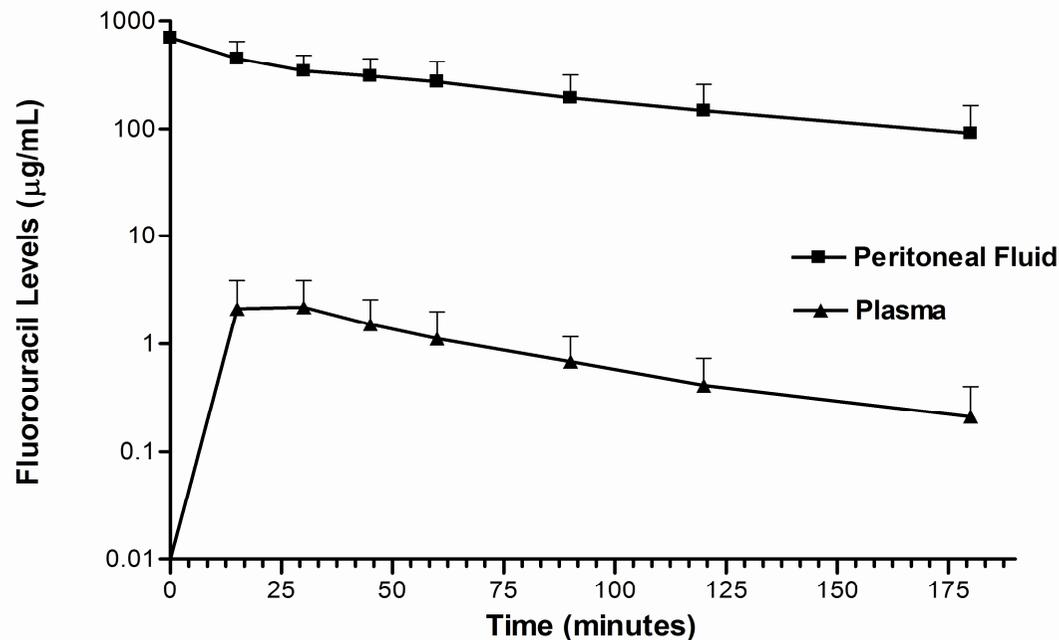
Study design : 5-FU pharmacology

Materials & Methods



Results : rationale for IP administration

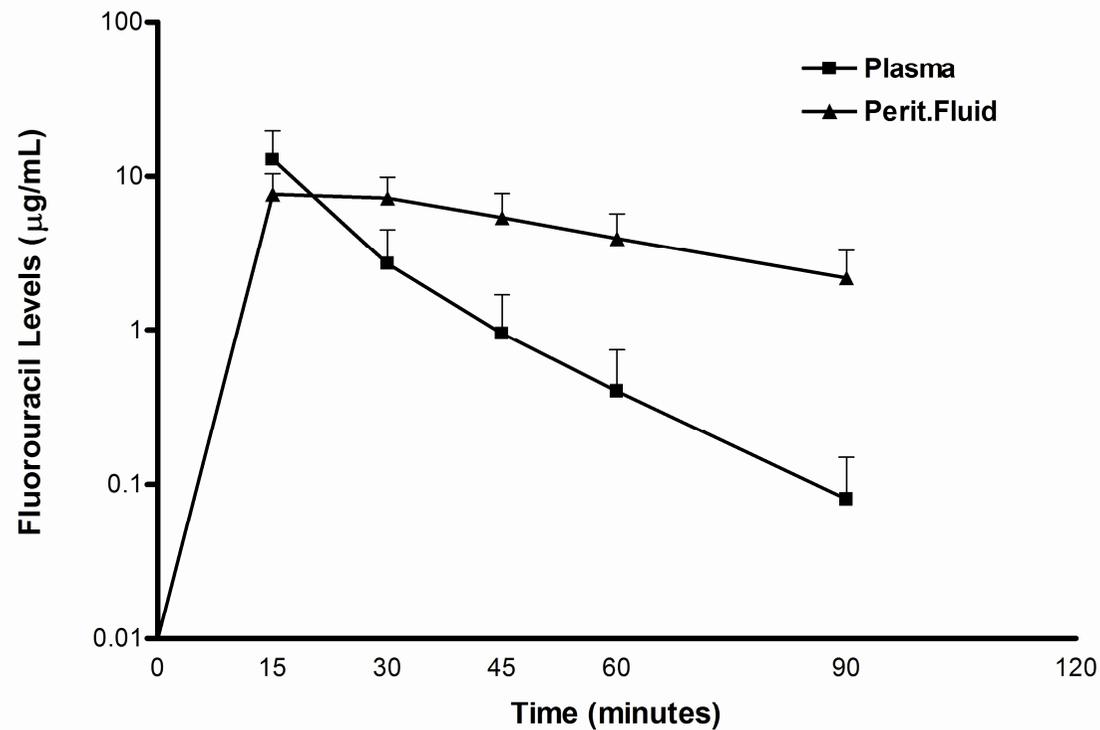
5-Fluorouracil concentrations in peritoneal fluid and plasma after early postoperative intraperitoneal chemotherapy administration (n=9). AUC IP/IV ratio = 422 (+/-360)



- Rapid metabolism outside peritoneal compartment by dihydropyrimidine-dehydrogenase
- Cell-cycle specific----repeated instillations

Results : rationale for IV administration

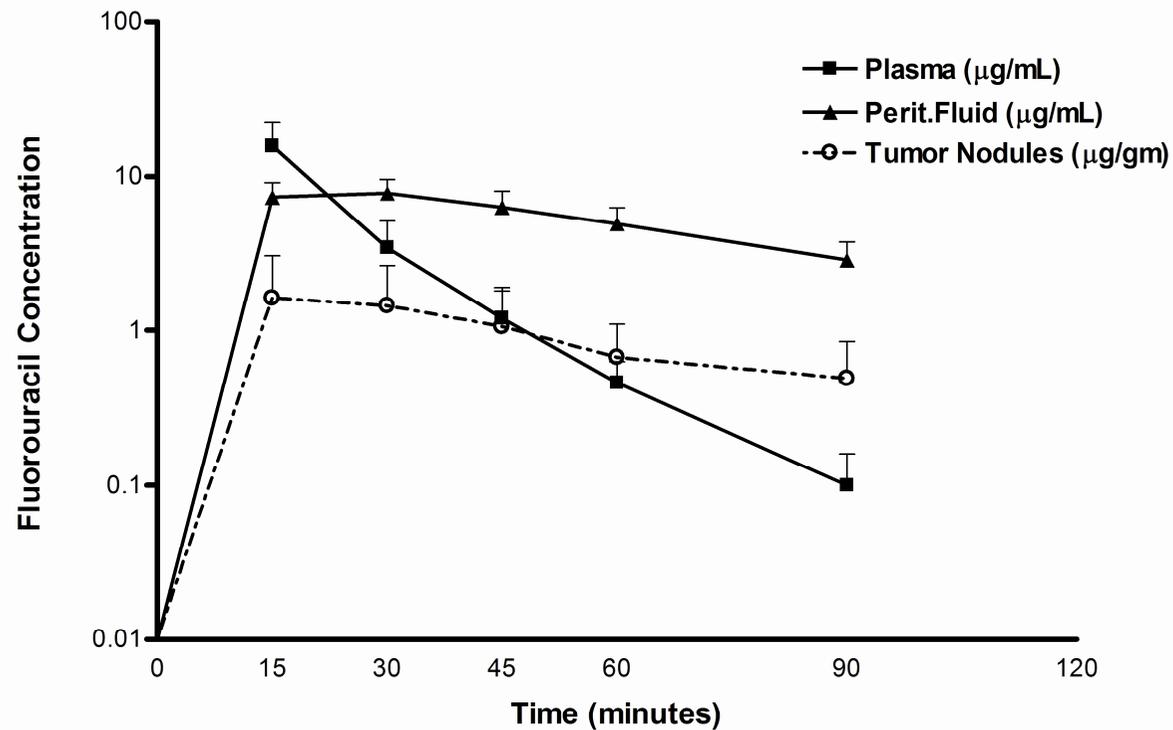
5-fluorouracil concentrations in peritoneal fluid and plasma after intravenous administration during HIPEC procedure (N=20).



- Rapid distribution to ALL body compartments
- Metabolization restricted to plasma compartment

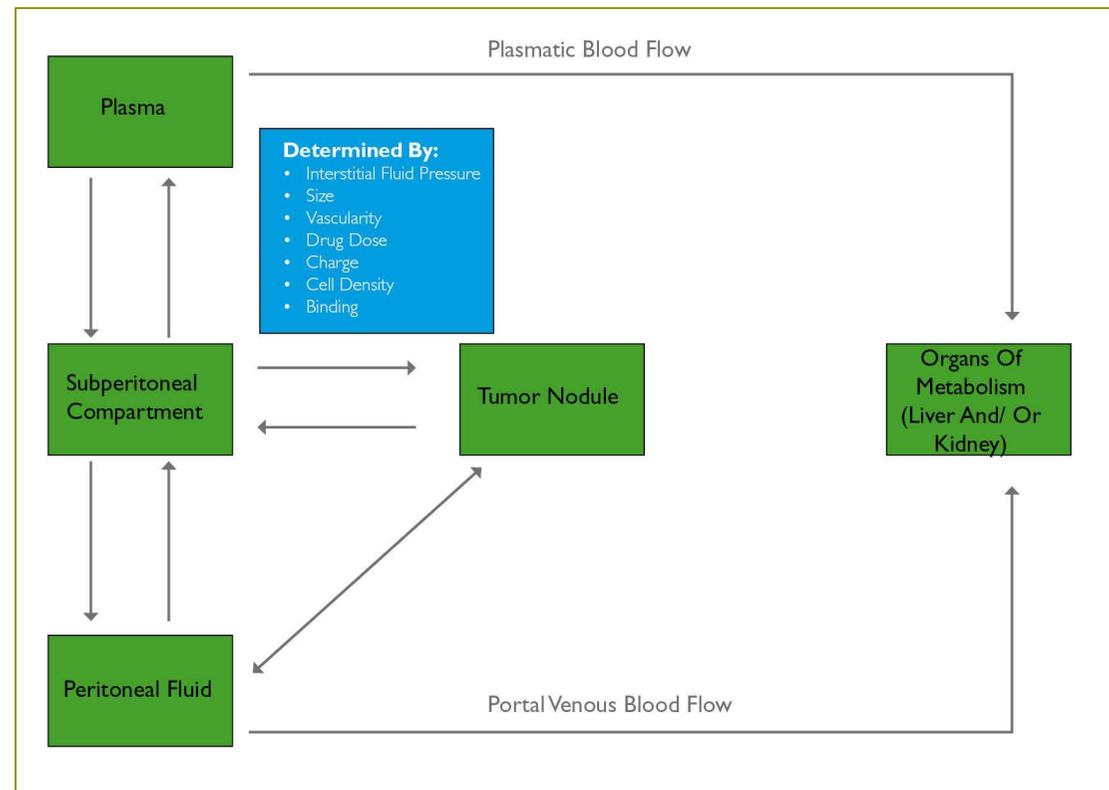
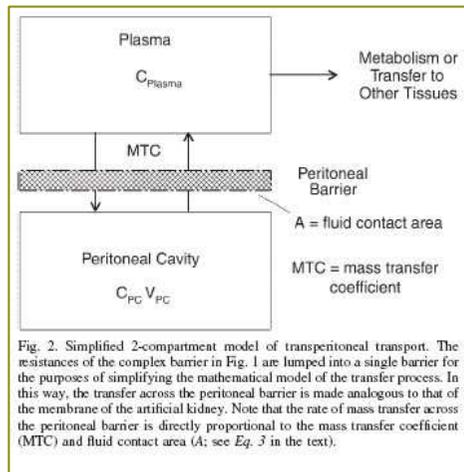
Results

5-Fluorouracil concentrations in plasma, peritoneal fluid and tumor nodules after intravenous administration during HIPEC procedure (N=9).

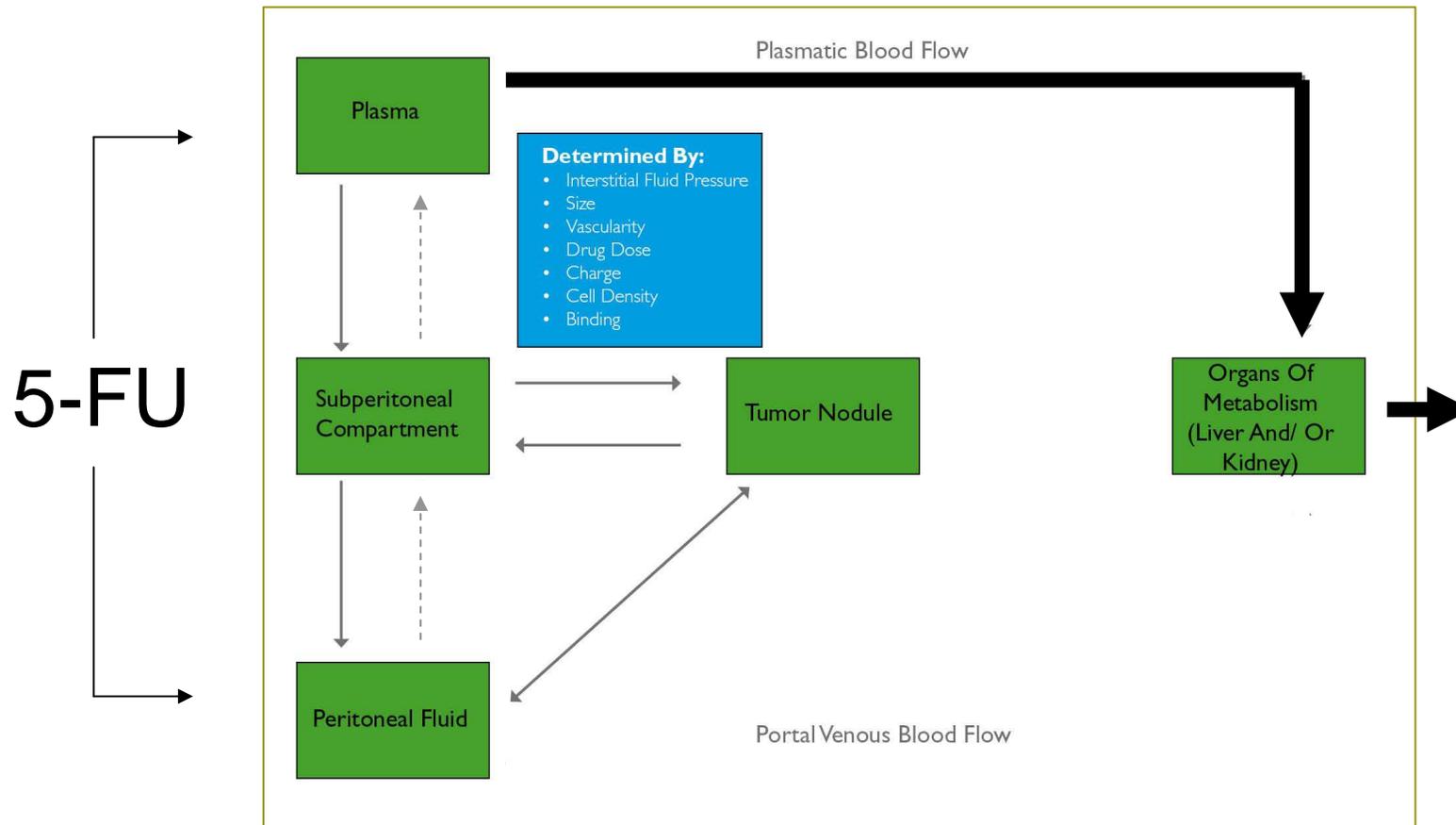


- Rapid distribution to ALL body compartments
- Metabolization restricted to plasma compartment

Conclusions: a revised pharmacokinetic model



Conclusions: a revised pharmacokinetic model



5-fluorouracil as a component of bidirectional intraoperative chemotherapy combines a rapid distribution phase with a selective metabolism confined for the most part to the vascular compartment.

Conclusions

- Timing of IV component of intraoperative chemotherapy = an important new variable

Large volume of artificial ascites is essential to the maintenance of high local-regional concentrations of 5-fluorouracil in the peritoneal fluid

Ideal situation for drug synergism by simultaneous IV and IP administration

Normothermally administered 5-fluorouracil becomes subject to the augmentation by mild hyperthermia

- Tumor nodule = pharmacologic endpoint of perioperative chemotherapy

Our data showing the concentrations of 5-fluorouracil in tumor nodules supports prior concepts that high intraperitoneal concentrations result in dose-augmentation.

Revision of the Dedrick-Flessner model is warranted