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Letters

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Portable Pumps in Cancer Chemotherapy: How to Deal With Marked Fluctuations in 5-Fluorouracil Blood Concentrations

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5-FLUOROURACIL (5-FU) is the major drug used in colorectal, breast and head and neck cancers. Several trials have demonstrated the superiority of 5-FU continuous infusion over intravenous bolus in terms of tolerance and response rate. Continuous administration of 5-FU is frequently delivered with battery-powered portable pumps that permit ambulatory treatment of patients. We previously [1] analysed 5-FU concentration blood profiles generated with portable and non-portable pumps during a 5 day continuous infusion of 5-FU and observed a significantly increased variability (more than 2-fold) in 5-FU plasma concentrations during the cycle when using portable pumps as compared with non-portable pumps (Table 1). Extreme values of 5-FU plasma concentrations obtained at steady state varied from undetectable (i.e. <5 ng/ml) up to 2300 ng/ml with portable pumps, whereas such extreme values were never observed with non-portable pumps. We thus strongly advised against the administration of 5-FU with portable pumps under usual conditions (pumps filled with undiluted 5-FU) and highlighted the fact that improvement of the 5-FU therapeutic index by dose adjustment based on pharmacokinetics [2, 3] was not feasible in this situation.

The explanation for this pharmacokinetic abnormality with portable pumps comes from the functioning of the pumps which deliver constant volumes (fixed by the pump) at regular time intervals depending on the programmed flow rate. Consequently, the greater the flow rate, the smaller the time interval between two pulses. In our previous study [1], the non-portable pumps (Vial Medical 8000 or Abbott Life Care 3, 1 l of diluted 5-FU changed daily) generated pulses every 14 or 6 s, respectively, whereas the portable pump (Pharmacia Cadd-1, 100 ml cassettes filled with undiluted 5-FU, 50 mg/ml, changed every 2–3 days) generated pulses every 1.8 to 4.5 min depending on the 5-FU dose administered. In fact, the theoretical variability of concentrations at steady state (ratio between maximal and minimal concentrations) is given by the following equation: C_{SS} max/C_{SS} min = $e^{kel \cdot \tau}$, kel being the elimination constant for a given drug and τ being a variable equal to the interval between two pulses [4]. Based on this pharmacokinetic law, the high kel value of 5-FU (approximately 4/h) due to its very short half-life (approximately 10 min) and the lengthened time interval between pulses generated by portable pumps explain, to a

*Table 1. Analysis of 5-FU plasma concentration for three administration modalities**

	Non-portable pumps†	Portable pumps: Filled with undiluted 5-FU† (100 ml cartridges changed every 2–3 days)	Portable pumps: Filled with diluted 5-FU (250 ml bags changed daily)
Number of patients	32	19	25
Number of cycles	32	25	34
Extreme values between cycles	20–650 ng/ml	<5‡–2300 ng/ml	37–862 ng/ml
Variability within the cycle			
Coefficient of variation (mean ± S.D.)	30% ± 21%	61% ± 44%	39.8% ± 22%
Statistics (Student *t*-test)		$P = 0.0006$	$P = 0.016$
		NS	

*Variability within the cycle evaluated by the coefficient of variation calculated on the four analysed concentrations; †previous data from [1]; ‡Limit of analytical detection.

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great extent, the wide variability encountered in 5-FU blood concentrations.

In order to maintain the feasibility of ambulatory treatment while reducing 5-FU blood concentration fluctuations, we prospectively tested a new administration modality by using Pharmacia Cadd-1 portable pumps adapted with 250 ml plastic bags filled with diluted 5-FU changed daily, so that the time interval between pulses (τ) was markedly reduced (every 17 s). A reduction in the C_{SS} max/C_{SS} min ratio could thus be expected from this new modality. 25 cancer patients (13 head and neck, 4 oesophagus, 8 colorectal) were included. Patients received a 5 day continuous infusion of 5-FU (starting dose 0.5–1 g/m^2/day). Thirty-four cycles were analysed. As previously described [1], blood samples were performed daily during the first 2 days of the cycle (8 a.m. and 5 p.m.) and 5-FU plasma concentrations were measured by HPLC [5]. Table 1 compares present results with our previous observations. The pharmacokinetic variability was significantly different between the three delivery modes (ANOVA, $P = 0.0005$). According to the pharmacokinetic law, when comparing the two administration modalities with the portable pump, the variability of the 5-FU concentration was significantly reduced with the new administration modality (using diluted 5-FU in 250 ml bags changed daily) and was very close to that observed with the classic non-ambulatory pumps.

Of practical, and probably also of clinical importance, is the fact that this new proposed administration modality leads to a satisfactory compromise between the feasibility of ambulatory treatment and the quality of 5-FU pharmacokinetic profiles which guarantees the security of treatment. Moreover, the increasingly used 5-FU dose adjustments based on pharmacokinetics remain feasible with portable pumps filled with diluted 5-FU (250 ml/day) whereas such dose adjustments were not applicable, and even more unsafe, under the usual conditions (portable pumps used with small cartridges filled with undiluted 5-FU).

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Intermittent Hormone Therapy in Prostate and Breast Cancers

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REPEATED CLINICAL responses to intermittent oestrogen therapy have been observed in patients with advanced prostate cancer [1], and suppression of PSA levels has been used to monitor intermittent treatment by a cyproterone–goserelin combination [2]. Oliver [3] recently refers to his group's experience with intermittent hormone therapy in prostate cancer, and suggests that the concept might possibly be relevant to other types of hormone-responsive cancer. In fact, similar observations have been reported both for intermittent stilboestrol and also for intermittent tamoxifen therapy in advanced breast cancer [4]. Stopping tamoxifen administration when regression of overt breast cancer lesions is complete, and not resuming it until reactivation manifests, has resulted in multiple responses and in hormonal control for periods of 6 to 8 years.

Continuous anti-oestrogen therapy may be a selective force for the development of hormone-resistant breast cancer. It is hypothesised that expression of growth-regulating oncogenes, such as *C-MYC* or *TP53*, permits escape from the inhibiting effect of tamoxifen, but that discontinuing therapy allows for a further response later. Many clinicians have noted response to a second course of tamoxifen therapy in patients with recurrence during, or subsequent to, adjuvant tamoxifen therapy, as long as an interval of 12–18 months is allowed to elapse between courses [5, 6]. Third and even fourth responses may be seen, although they are usually of shorter duration. It is time to set up randomised trials of intermittent hormonal therapy in breast as well as in prostate cancer. The received wisdom that the widely used agent tamoxifen is most effective when given continuously for a protracted time period needs testing [7].

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