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).

1. Etienne M-C, Milano G, Lagrange JL, *et al.* Marked fluctuations in drug plasma concentrations caused by the use of portable pumps for fluorouracil continuous infusions. *J Natl Cancer Inst* 1993, **85**, 1005–1007.
2. Santini J, Milano G, Thyss A, *et al.* 5-FU therapeutic monitoring with dose adjustments leads to an improved therapeutic index in head and neck cancer. *Br J Cancer* 1989, **59**, 287–290.
3. Milano G, Etienne M-C, Renée N, *et al.* Relationship between fluorouracil systemic exposure and tumor response and patient survival. *J Clin Oncol* 1994, **12**, 1291–1295.
4. Ritschel WA. Multiple dose pharmacokinetics. In Ritschel WA, ed. *Handbook of Basic Pharmacokinetics*. Hamilton, Illinois, U.S.A., Drug Intelligence Publication Inc., 1980, 249–273.
5. Christophidis N, Mihaly G, Vajda F, *et al.* Comparison of liquid- and gas–liquid chromatographic assays of 5-fluorouracil in plasma. *Clin Chem* 1979, **25**, 83–86.

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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].

1. Klotz LH, Herr HW, Morse MJ, *et al.* Intermittent endocrine therapy for advanced prostate cancer. *Cancer* 1986, **58**, 2546–2550.
2. Akakura K, Bruchovsky N, Goldenberg SL, *et al.* Effects of intermittent androgen suppression on androgen dependent tumors. *Cancer* 1993, **71**, 2782–2790.
3. Oliver RTD. New directions with hormone therapy in prostate cancer; possible benefit from blocking prolactin and use of hormone treatment intermittently in combination with immunotherapy. *Eur J Cancer* 1995, **31A**, 859–860.
4. Stoll BA. Rechallenging breast cancer with tamoxifen therapy. *Clin Oncol* 1983, **9**, 347–351.
5. Muss HB, Smith R, Cooper MR. Tamoxifen rechallenge; response to tamoxifen following relapse after adjuvant chemohormonal therapy for breast cancer. *J Clin Oncol* 1987, **5**, 1556–1558.

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6. Pronzato P, Ardizzoni A, Lionetto R, *et al.* Tamoxifen rechallenge. *J Clin Oncol* 1988, 6, 751–752.
7. Stoll BA. Overprolonged adjuvant tamoxifen therapy. *Ann Oncol* 1991, 2, 401–403.

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Granulocyte–Macrophage Colony-stimulating Factor Therapy in Patients With Chemotherapy-induced Aplasia and *Clostridium difficile* Enterocolitis

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THE PROPHYLACTIC administration of recombinant human granulocyte–macrophage colony-stimulating factor (rhu-GM-CSF) is well established in cancer patients. Neutropenic periods are shortened resulting in reduced frequency of septic complications [1–4]. Although beneficial effects have been reported by several authors [5–7], the interventional use of rhu-GM-CSF in neutropenic patients with established septic complications remains controversial. This report documents clinical effects and safety of rhu-GM-CSF treatment in two paediatric cancer patients with neutropenic enterocolitis, caused by *Clostridium difficile*.

An 18-year-old patient with osteosarcoma of the pelvis was treated with ifosfamide 3 g/m^2 on days 1 and 2 and cisplatinum 120 mg/m^2 on day 3. On day 6, he developed septic fever with bone marrow aplasia [white blood cell count (WBC) 400/μl, absolute neutrophil count (ANC) 24/μl], C-reactive-protein (CRP) was 7 mg/dl (normal <0.5 mg/dl) and empiric therapy with piperacillin and gentamicin was begun. Cefamandole was added the next day as fever did not resolve. On day 8, he had loose stools, so oral vancomycin therapy and rhu-GM-CSF 5 μg/kg/day subcutaneously was started. In addition, the antimicrobial regimen was changed to amikacin and ceftazidime on day 9. Stool cultures revealed *C. difficile* and toxin assays were positive. Over the next 2 days, the patient had septic temperatures with now frequent blood-stained stools, and on day 11 developed acute abdominal pain and tenderness, CRP rose to 10.3 mg/dl. Diagnosis of severe enterocolitis was confirmed by ultrasonography which showed thickening of the wall of the whole colon. Dramatic clinical improvement occured together with reconstitution of WBC (ANC 745/μl) on day 12. rhu-GM-CSF was continued until day 15 for a total of 8 days and cancer chemotherapy was continued only 1 day behind schedule on day 23 (Figure 1a).

A 5-year-old girl with meningeal sarcoma was treated with vincristine 1.5 mg/m^2 on day 1, and etoposide 150 mg/m^2, ifosfamide 2 g/m^2 and doxorubicin 20 mg/m^2 on days 1, 2 and 3. On day 9, she had bone marrow aplasia (leucocytes 900/μl, ANC 108/μl) and complained of severe colic abdominal pain, showing meteorism and hyperperistalsis, CRP was 4.9 mg/dl. The next day she developed fever up to 39.2°C, CRP rose to 10.4 mg/% and she had frequent (six per day) loose stools. Physical examination showed tenderness of the right lower abdominal quadrant. Empiric antimicrobial therapy was started with imipenem and gentamicin, and a course of oral vancomycin was given for 10 days. Daily subcutaneous injections of rhu-GM-CSF 5 μg/kg body weight were given from day 10 to 14. *C. difficile* enterocolitis was confirmed by positive toxin assays. Temperature declined to normal after 2 days, but diarrhoea persisted until day 13. Leucocyte recovery (WBC 2800/μl, ANC 1480/μl) on day 14 was paralleled by complete reconstitution of the patient's clinical condition. Cancer chemotherapy was continued on day 22 without delay (Figure 1b).

C. difficile enterocolitis represents a life-threatening infectious complication for neutropenic cancer patients with mortality rates around 30–50% [8]. Severe and prolonged leucopenia and neutropenia is an important cofactor for the development and course of this infection [8, 9]. Pathological mechanisms of *C. difficile* enterocolitis are attributed to a selection and overgrowth of these pathogens by alteration of bacterial flora and to the

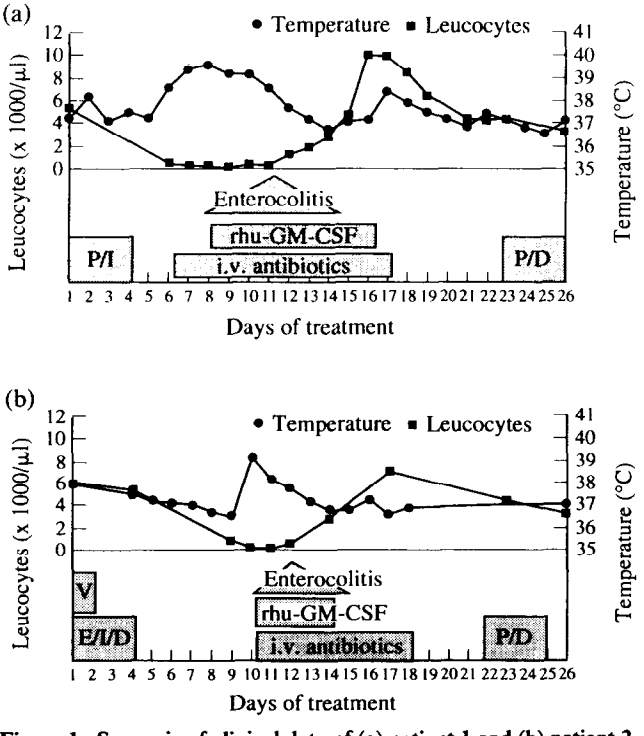

Figure 1. Synopsis of clinical data of (a) patient 1 and (b) patient 2. Capitals within the shaded rectangles refer to cytostatic therapy. P, cisplatinum; I, ifosfamide; D, doxorubicin; E, etoposide; V, vincristine.

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