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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

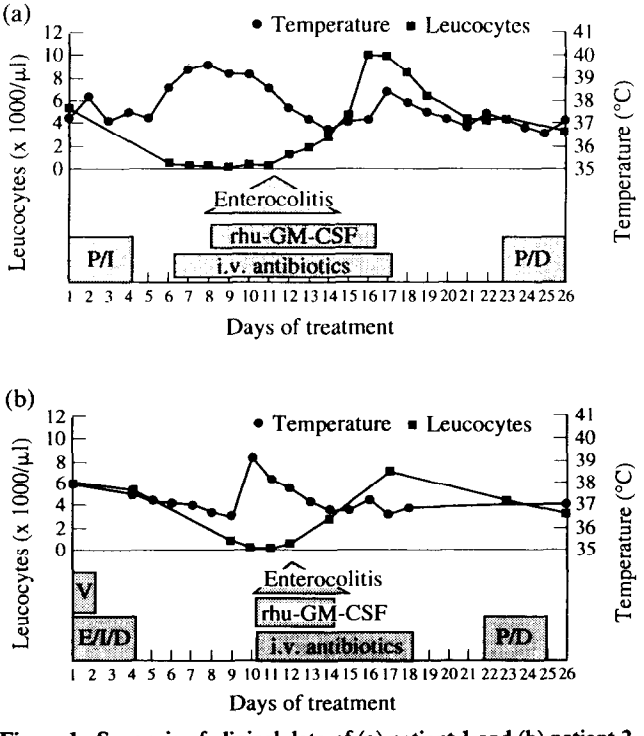

Figure 1. Synopsis of clinical data of (a) patient 1 and (b) patient 2. Capitals within the shaded rectangles refer to cytostatic therapy. P, cisplatinum; I, ifosfamide; D, doxorubicin; E, etoposide; V, vincristine.

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toxicity of the *C. difficile* toxins [10]. The release of interleukin-1 (IL-1) and tumour necrosis factor (TNF) from monocytes induced by these toxins may contribute to the bowel inflammation [11]. Recently, Vlasveld and associates [12] suggested that GM-CSF might be a cofactor in the pathogenesis of enterocolitis. Experimental data on *C. difficile* toxins A and B showed that they strongly induce release of TNF, IL-1 and IL-6 by monocytes [11]. The fact that rhu-GM-CSF itself induces TNF release from monocytes may have led them to their hypothesis [13]. Maximum TNF levels were observed 3–4 days after rhu-GM-CSF application in neutropenic patients [14]. Despite these theoretical drawbacks, the administration of rhu-GM-CSF was associated with prompt resolution of safe granulocyte counts and prompt recovery from enterocolitis in our patients.

Apparently, the positive effect of rapid restoration of a functionally active granulomonocytic defense system by far outweighs theoretical shortcomings of secondary cytokine release.

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Short-term Versus Continuous Infusion: No Influence on Ifosfamide Side-chain Metabolism

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IFOSFAMIDE (IFO) is a widely used anticancer drug which requires metabolic activation by hydroxylation of the ring system to exert cytotoxic activity. A second metabolic pathway produces the cytostatically inactive metabolites, 2-dechloroethylifosfamide (2-D-IFO) and 3-dechloroethylifosfamide (3-D-IFO), releasing chloro-acetaldehyde. This pathway of side-chain metabolism has been discussed as a source of CNS toxicity [1–3] and in connection with renal toxicity [4]. As regards neurotoxicity, the incidence seems to be strongly schedule-dependent [5]. However, antitumour efficacy was also lower in patients on a continuous IFO application schedule [6].

We, therefore, compared the urinary exception of IFO, 2-D-IFO and 3-D-IFO on short-term and continuous ifosfamide infusion (3g/m²/daily). In 13 children, of whom 6 received IFO by 1 h infusion and 7 by continuous infusion, urine output up to 72 h was completely sampled and investigated by gas chromatography (Figure 1).

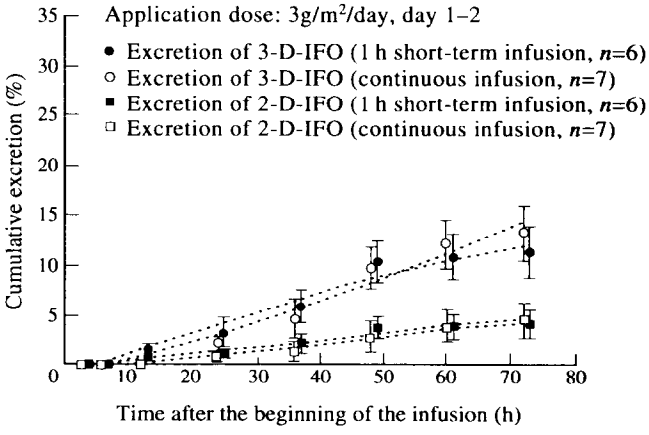

Figure 1. Cumulative excretion of side-chain metabolites (in % of the totally applied dose).

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