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# Letters

## Problems Associated with the Study of Cytokines in Patients with Leukaemia

H.D. Preisler and A. Raza

THE CLINICAL USE of cytokines may favourably alter the proliferative behaviour of leukaemia cells. The lack of a consistent relation between the cell cycle characteristics of leukaemia cells and the course of the disease or treatment outcome results from two problems inherent to cell cycle studies. First is the inaccuracy of the assessments of the per cent cells in S-phase due to variable dilution of marrow aspirate cells by peripheral blood cells 2–4. Then, even if an accurate labelling index (Li) were available, the data would still be of marginal interest since the most important characteristic is length of the cell cycle [4].

One attempt to overcome the problem of dilution by peripheral blood is to estimate the extent of dilution [4]. Other approaches include the release of cells from marrow biopsy samples by shaking or enzymatically [1,2]. While these approaches demonstrated that many more cells were in S-phase than had been observed when aspirates were used, there has been no demonstration that all marrow cells are released or that the released cells are representative. To avoid these problems, we administer halogenated pyrimidines embed marrow biopsy specimens in plastic and use monoclonal antibodies to identify S-phase cells [4]. Our studies demonstrate that use of cells "released" from biopsy samples underestimates the proportion of leukaemia cells in S-phase [5]. We use Li with measurement of the duration of S-phase (Ts) to calculate cell cycle time (Tc).

Patient 1 (Table 1) did not receive any cytokine. The biopsy Li, Ts and Tc were unchanged over the 3 days of study. But if the aspirate Li is used, there would appear to be a 235% increase in Li. If this Li is used to calculate Tc, the proliferative rate of the leukaemia cells would seem to have dramatically increased. Also if the spuriously low aspirate Li is used, Tc is extremely long. Patient 2 received a 3 day course of retinoic acid and interferon [5]. Li fell in both the aspirate and biopsy samples. Unexpectedly, however, Ts also fell, i.e.an acceleration of the proliferative rate rather than a slowing as would have been concluded if only Li was used. Patient 3 received recombinant human granulocyte–macrophage colony-stimulating factor (rhGM-CSF). While the aspirate Li doubled, that of the biopsy specimen fell. Ts was slightly prolonged. Thus, rhGM-CSF was associated with a slowing of the leukaemia cell proliferative rate and not with acceleration, as would have been concluded if marrow aspirate data had been used. These paradoxical effects are not rare.

Thus, it is impossible to measure accurately the effects of cytokines on leukaemia cell proliferation *in vivo* unless intact marrow biopsy specimens are used and unless Ts and Li are used to calculate Tc. The use of peripheral blood in these studies[6] further confounds the issue since apparent alterations in the kinetics of the cells in this compartment can be the result of the mobilisation of immature cells from the marrow and other sites of proliferation rather than an effect on cell proliferation.

The failure to use appropriate methods in studies of cytokines will have a negative impact since inaccurate and/or incomplete cell cycle data will lead to erroneous conclusions about the effects of these agents and their clinical usefulness. Unfortunately, none of the reported studies of the effects of cytokines on leukaemia cell proliferation used methods capable of providing accurate and complete data [6–9].

1. Preisler HD, Raza A, Larson R, *et al.* Some reasons for the lack of progress in the treatment of acute myelogenous leukaemia. *Leuk Res* 1991, **15**, 773–780.
2. Dosik GM, Barlogie B, Goldie W, Johnston D, Tekell JL, Drewinko B. Flow cytometry of DNA content in human bone marrow: a critical reappraisal. *Blood* 1980, **55**, 734–740.
3. Hiddemann W, Buchner W, Andreef M, Wormasen B, Melamed MR, Clarkson BO. Bone marrow biopsy instead of "marrow juice" for cell kinetic analysis: comparison of bone marrow biopsy and aspiration material. *Leuk Res* 1982, **6**, 601–612.
4. Raza A, Maheshwari Y, Preisler HD. Differences in cell cycle characteristics amongst patients with acute nonlymphocytic leukaemia. *Blood* 1987, **69**, 1647–1653.
5. Preisler HD, Raza A, Hulette B, *et al.* The use of biologically active agents in the treatment of AML and other neoplastic diseases. *Status of Differentiation Therapy*, Volume 2, 1991. In press.
6. Bettelheim P, Valent M, Andreef A, *et al.* Recombinant human granulocyte macrophage colony-stimulating factor in combination with standard induction chemotherapy in *de novo* acute myeloid leukaemia. *Blood* 1991, **77**, 700–711.
7. Tafuri B, DeFelice MC, Petti A, *et al. In vivo* and *in vitro* cell kinetic effects of rhGM-CSF in the combined cytokine-chemotherapy treatment of acute myeloblastic leukaemia. *Haematologica* **76**, suppl 4, 10/91, abstract 128.
8. LaCombe F, Dumain P, Puntous M, *et al.* Clinical and biological results in acute myeloid leukaemia patients treated with GM-CSF and intensive therapy. *Haematologica* **76**, suppl 4, 10/91, abstract 139.
9. Buchner T, Hiddemann W, Wormann B, *et al.* Recombinant human GM-CSF priming and long term administration together with multiple course chemotherapy vs CT alone in newly diagnosed acute myeloid leukemia. *Blood* **78**, 10, suppl 1, 11/91, abstract 641.

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## Handedness and Breast Cancer

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THE REPORT by Olsson and Ingvar [1] that left handedness is uncommon in breast cancer patients fails to mention a possible

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important cause for this finding. A recent study in California by Halpern and Coren [2] on handedness and life-span has shown that the mean age of death in left-handed people is 9 years earlier than in right handers. The reason for this 9-year reduction in life span is unknown, but may be related to the fact that left-handed (and left-footed) people live in a right-handed world, and are more prone to accidental death. Breast cancer is primarily a disease of older age groups. Perhaps fewer left-handed women live long enough to develop breast malignancy. Whether the numbers of patients involved are sufficient to account for Olssen and Ingvar's findings remains to be determined.

1. Olsson H, Ingvar C. Left handedness is uncommon in breast cancer patients. *Eur J Cancer* 1991, 27, 1694–1695.
2. Halpern DF, Coren S. Handedness and life span. *N Engl J Med* 1991, **324**, 998.

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# Cisplatin-induced Sodium and Magnesium Wastage

## Anne Ørbo and Ernst Simonsen

SELECTIVE RENAL wasting of magnesium combined with hypomagnesaemia is a frequent side-effect after treatment with cisplatin [1]. However, hyponatraemia is rare: persisting hyponatraemia has been reported in only 3 patients, all children [2, 3].

We report a case of severe, persisting hyponatraemia and hypomagnesaemia in a 53-year-old Lapp woman treated with cisplatin for adenocarcinoma of the endometrium. A simple hysterectomy and bilateral oophorectomy was initially performed. Histological examination revealed a low differentiated (grade III) tumour infiltrating deeply in the uterine wall, affecting the upper part of the cervix. The patient was admitted to the University Hospital to receive adjuvant therapy consisting of external pelvic radiation (total dose 44 Gy), followed by four single courses of cisplatin 50 mg/m$^2$ plus epirubicin 50 mg/m$^2$ every 4 weeks. The second course was given in the local hospital and the last course was cancelled. Serum creatinine and creatinine clearance were always normal. The concentrations of Na, K and Mg (in mmol/l) were: 137, 4.0 after course one (magnesium not determined); 112, 1.2 and 0.47 after course two; and 109, 2.5 and 0.3 after course three. Serum values 3 months after the last course remained low.

Many side-effects of cisplatin have been described [2]. Nephrotoxicity, which is dose-limiting, may be manifested as azotaemia, hypokalaemia, hypocalcaemia and hypomagnesaemia [1, 4–6]. Our case is unusual, with persistent hyponatraemia with hypokalaemia and hypomagnaesemia after three single low-dose courses of cisplatin, a cumulated dose of 140 mg.

Electrolyte wasting is thought to have its origin in tubular damage with destruction of the electrolyte regulating mechanisms in the nephrons [4–6]. The sites of cation reabsorption are those that are most sensitive to the toxic effects of cisplatin [2]. Whereas renal regulation of calcium and magnesium excretion is similar to that of sodium in the proximal part of the duct system, the transport mechanisms in the distal part seem to be independent and different. Cisplatin-induced nephrotoxicity may be due to a proximal tubule impairment [1]. Thus, hyponatraemia should be as frequent as hypokalaemia and hypomagnaesemia. However, this is the first report of a persisting hyponatraemia in an adult after cisplatin. The fact that the patient was of a special ethnic origin may be important and a pharmacogenetic mechanism should be considered.

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1. Daugaard G, Abildgaard U. Cisplatin nephrotoxicity. A review. *Cancer Chemother Pharmacol* 1989, **25**, 1–9.
2. Lammers PJ, White L, Ettinger LJ. Cis-platinum induced renal sodium wasting. *Med Pediatr Oncol* 1984, **12**, 343–346.
3. Vassal G, Rubie H, Kalifa C, Hartmann O, Lemerle J. Hyponatremia and renal sodium wasting in patients receiving cisplatinum. *Pediatr Hematol Oncol* 1987, **4**, 337–344.
4. Blachley JD, Hill JB. Renal and electrolyte disturbances associated with cisplatin. *Ann Intern Med* 1981, **95**, 628–632.
5. Schilsky RL, Barlock A, Ozols RF. Persistent hypomagnesemia following cisplatin chemotherapy for testicular cancer. *Cancer Treat Rep* 1982, **66**, 1767–1769.
6. Lyman NW, Hemalatha C, Viscuso RL, Jacobs MG. Cisplatin-induced hypocalcemia and hypomagnesemia. *Arch Intern Med*, 1980, **140**, 1513–1514.

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# Lethal Toxic Epidermal Necrolysis During Suramin Treatment

## G. Falkson and B.L. Rapoport

WE READ with interest May and Allolio's [1] report of fatal epidermal necrolysis during suramin therapy as we recently reported this in a patient being treated with suramin [2]. 10 of the first 17 patients we treated with suramin developed skin toxicity of varying severity. We treated a further 29 patients giving hydrocortisone sodium succinate 200 mg intravenously before suramin administration and saw only one mild skin reaction in these patients. It therefore seems appropriate to consider giving corticosteroids before suramin.

1. May E, Allolio B. Fatal toxic epidermal necrolysis during suramin therapy. *Eur J Cancer* 1991, **27**, 1338.
2. Rapoport BL, Falkson G, Ansell SM, Lotz BP, de Wet M. A phase II clinical study of suramin in combination with mitomycin C in patients with non small cell lung cancer. *Lung Cancer* 1991, 7, 323–328.

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