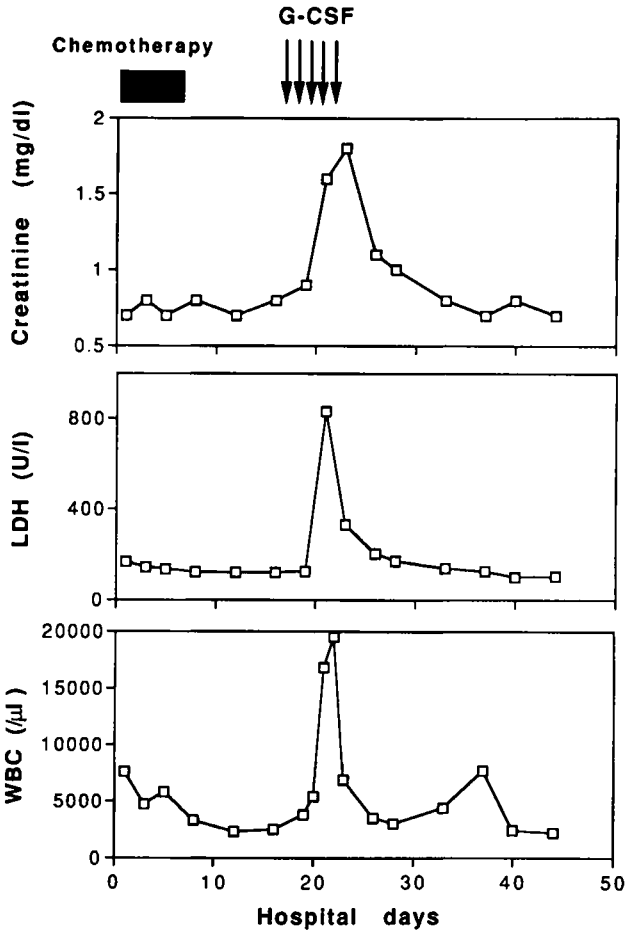

Fig. 1. Changes in WBC counts, and in serum creatinine and LDH levels.

An 18-year-old Japanese man was referred to Akita University Medical Center for peripheral blood stem cell transplantation (PBSCT). He had undergone surgical resection of cecum and terminal ileum because of ileus and lower gastrointestinal bleeding, and had been diagnosed as having diffuse large-cell lymphoma with a B cell phenotype. Regional lymph nodes were involved, but there was no evidence of involvement of other lymphatic systems or organs. He had received three cycles of intensive chemotherapy based on vinca alkaloids, cyclophosphamide, anthracylines, etoposide, and prednisolone after surgery. The patient had no history of renal diseases or any allergy to drugs, and had never shown renal impairment during the previous chemotherapy.

On admission to our hospital, the patient remained in remission with normal serum creatinine, blood urea nitrogen, and uric acid levels (Fig. 1). He received intensification chemotherapy consisting of adriamycin, cytosine arabinoside, vindesine, and prednisolone for 5 days, and then subcutaneous injection of G-CSF (filgrastim) at 150 μg/day was begun on the seventeenth day of chemotherapy for harvesting PBSC. On the fifth day of G-CSF administration, the patient had fever (38.3°C), and sharp rises in WBC counts and LDH concentrations were observed. These changes were accompanied by an increase in serum creatinine levels (Fig. 1). There were no abnormalities in urinary proteins and sediments, but urine volume slightly decreased down to 800 ml/day, despite no alteration in oral intake. Serum uric acid and phosphate levels were 8.1 mg/dl and 5.3 mg/dl, respectively. The patient did not receive any nephrotoxic drugs such as aminoglycosides. After discontinuation of G-CSF administration, serum creatinine and LDH concentrations rapidly returned to normal levels. PBSC collection was done in the recovery phase of this course of chemotherapy, and PBSCT was successfully performed thereafter. When the patient underwent PBSCT, he received lower doses of G-CSF (75 μg/day) and did not show renal impairment. At present the patient remains in remission with normal creatinine values.

We are not ready to provide a good explanation for the transient renal impairment observed following G-CSF treatment in this case. However, it is possible that leukostasis in the kidneys during G-CSF therapy might be the cause. To our knowledge, this is the first reported case presenting renal impairment during leukocytosis induced by G-CSF administration. It is important to be aware of this adverse effect, particularly when this agent is given to patients with preexisting renal diseases.

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References

1. Maiche AG, Muhonen T, Porkka K: Lactate dehydrogenase changes during granulocyte colony-stimulating factor treatment. Lancet 340:853, 1992.
2. Fossa SD, Poulsen JP, Aaserud A: Alkaline phosphatase and lactate dehydrogenase changes during leukocytosis induced by G-CSF in testicular cancer. Lancet 340:1544, 1992.

In Vitro Effects of a Combination of Zidovudine and Acyclovir on Growth of Normal Human Myeloid Progenitor Cells

To the Editor: In recent years, the combined administration of zidovudine (ZDV) and acyclovir (ACV) to patients with adult immunodeficiency syndrome (AIDS) has gained importance, mainly due to its beneficial survival effect [1,2]. However, as myeloid suppression is one of the main adverse effects of ZDV, the effect of cotherapy with ZDV and ACV on bone marrow myeloid progenitors as compared to ZDV alone is still controversial [1,3,4].

In the present study, the in vitro effects of combined administration of ZDV and ACV at various concentrations on the growth of normal human myeloid progenitor cells were evaluated.

Normal bone marrow samples were obtained from the anterior ribs of 5 patients undergoing explorative thoracotomy. Informed, written consent was obtained from all patients. The rib cavity was washed with α medium (Flow Laboratories, Glasgow, Scotland) containing 10% fetal calf serum (FCS) (Hyclone Laboratories, Logan, UT). The cells were laid over Ficoll-Hypaque gradient. The mononuclear cells were collected from the interphase and washed twice with phosphate-buffered saline (PBS), pH 7.4. Thereafter, 2×10^5 cells were seeded in 1-ml aliquots of α medium containing 15% FCS (pretested), 0.3% Bacto-agar (Difco Laboratories), plus 75-μl placenta-conditioned medium (as a source of colony-stimulating factor) in 35-mm plastic petri dishes. ZDV in concentrations of 0.5, 1.0, 5.0, and 10 μg/ml, and ACV in concentrations of 2 and 20 μg/ml (both diluted in α medium) were added to the dishes. Three replicate culture plates were incubated for 10–14 days in humidified atmosphere with 5% CO_2 at 37°C. Colonies consisting of 50 or more cells were scored as colony forming units-granulocyte macrophage (CFU-GM), using an inverted mi-

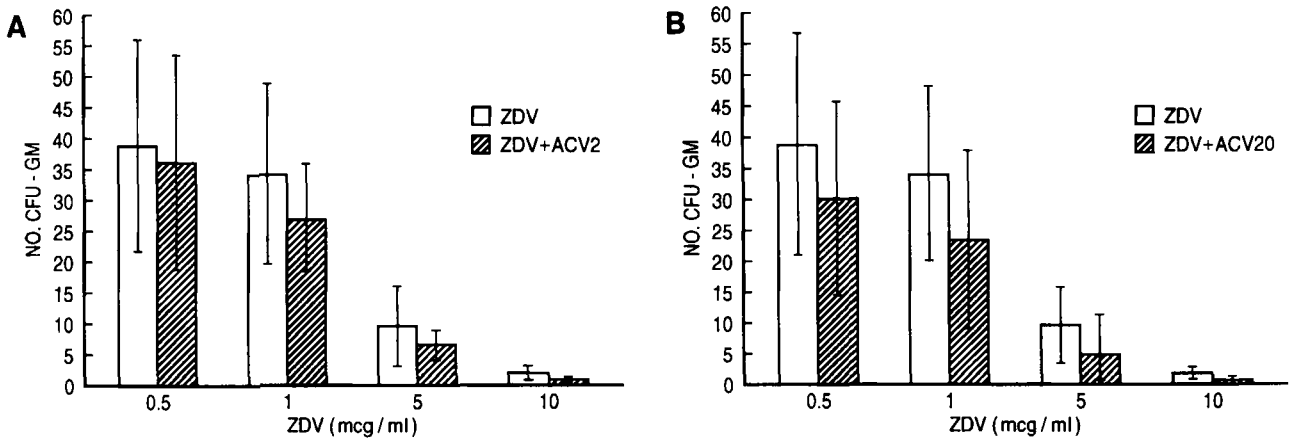

Fig. 1. Effect of 2 μg/ml acyclovir (ACV2) (A) and of 20 μg/ml acyclovir (ACV20) (B) in combination with ZDV on colony formation of normal human bone marrow (±SD).

croscope. The Wilcoxon rank sum test was used for statistical analysis, while two-sided P value at α level <0.05 was considered statistically significant.

Study results showed a significant linear dose-related suppression in the number of myeloid colony-forming units with the addition of increasing concentrations of ZDV (mean CFU-GM count of 38, 35, 10, and 2 following exposure to ZDV doses of 0.5, 1.0, 5.0, and 10.0 μg/ml, respectively, vs. mean control CFU-GM count of 42 colonies). ACV alone in different concentrations had no effect on the CFU-GM count. In cells exposed both to ZDV and ACV in a concentration of 2 μg/ml, there was an insignificant decrease in the mean number of CFU-GM as compared to ZDV alone (Fig. 1A). At a higher concentration of ACV (20 μg/ml) (Fig. 1B), the combination of ZDV and ACV further decreased colony growth in comparison to ZDV alone, on the border of statistical significance ($P = 0.06$).

The findings in the present study in normal subjects support other observations that the effect of a combination of ZDV and ACV on both pluripotent and committed hemopoietic progenitors does not potentiate the hemotoxicity of the latter [5]. The myelosuppression observed even when high doses (20 μg/ml) of ACV were added to ZDV did not differ significantly ($P = 0.06$) from the effect of ZDV alone. However, it is plausible that with increased sample size the differences would have become statistically significant. The addition of lower doses of ACV (2 μg/ml) clearly did not alter the myelosuppression induced by AZT alone ($P = 0.18$). The present results are supported by the recent findings of Cooper et al. [1], who compared the efficacy and safety of ZDV at a maintenance dose of 250 mg every 6 hr alone or as cotherapy with high doses ACV (800 mg every 6 hr).

In summary, although the present study showed that the addition of increasing doses of ACV to ZDV did not significantly change the myeloid suppression associated with the administration of ZDV alone, further studies with greater sample size and increased statistical power should be conducted to further clarify this issue.

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REFERENCES

1. Cooper DA, Pehrson CP, Pedersen C, Moroni M, Oksenhendler E, Rozennbaum W, Clumeck N, Faber V, Stille W, Hirschel B, Farthing C, Doherty R, Yeo JM, European-Australian Collaborative Group: The efficacy and safety of zidovudine alone or as cotherapy with acyclovir for the treatment of patients with AIDS and AIDS-related complex: A double-blind, randomized trial. AIDS 7:197, 1993.
2. Stein DS, Graham NMH, Park LP, Hoover DR, Phair JP, Detels R, Ho M, Saah AJ: The effect of the interaction of acyclovir with zidovudine on progression to AIDS and survival. Ann Intern Med 121:100, 1994.
3. Bogliolo G, Lerza R, Mencoboni M, Saviane A, Pannacciulli I: Azidothymidine-induced depression of murine hemopoietic progenitor cells. Exp Hematol 16:938, 1988.
4. Surbone A, Yarchoan R, McAtee N, Blum MR, Maha M, Allain JP, Thomas RV, Mitsuya H, Lehrman SN, Leuther M, Pluda JM, Jacobsen FK, Kessler HA, Myers CE, Broder S: Treatment of the acquired immunodeficiency syndrome (AIDS) and AIDS-related complex with a regimen of 3′-azido-2′-3′-dideoxy thymidine (azidothymidine or zidovudine) and acyclovir. Ann Intern Med 108:534, 1988.
5. Bogliolo G, Lerza R, Mencoboni M, Flego G, Gasparini L, Pannacciulli I: Hemotoxic effects on mice of combined administration of azidothymidine and acyclovir. Exp Hematol 19:838, 1991.

Decreased Lymphocytic Proliferation by Mitogens in Patients With Transitional Cell Carcinoma of the Renal Pelvis Subsequent to Non-Hodgkin's Lymphoma

To the Editor: Increased risk of bladder tumor after cyclophosphamide administration has been previously reported [1,2]. It has been suggested that urinary acrolein, which is a degradative product of cyclophosphamide, is associated with the development of transitional cell carcinoma [3]. We noted that development of renal pelvic tumor in a patient who had undergone chemotherapy, including cyclophosphamide. Of particular interest, his T cell function seemed to be abnormal, and therefore we present this case.

A 72-year-old man was diagnosed as having non-Hodgkin's lymphoma in January 1988 (Fig. 1a). He had smoked one pack of cigarettes daily for many years. He was administered three courses of chemotherapy, which consisted of cyclophosphamide, doxorubicin, vincristine, and prednisolone. He received seven additional courses of therapy, in which vindesine was