To determine whether cell killing could be responsible for the drop in circulating lymphocytes, mononuclear cells from the patient were cultured for 72 hours in presence of increasing concentrations of naproxen or etodolac up to 240 μM and analyzed at 24, 48, and 72 hours for the binding of monoclonal antibody to internucleosomal DNA by enzyme-linked immunosorbent assay (ELISA) as a measure of apoptosis using a standard kit assay (Cell Death Detection ELISA Plus, Boehringer-Mannheim, Indianapolis, IN). No significant enhancement of apoptosis was achieved by etodolac compared with naproxen (data not shown). The same results were obtained in a separate experiment when assayed by analysis of the binding of FITC annexin V to and the uptake of propidium iodide by the patient’s mononuclear cells by flow cytometry (data not shown). The fact that an increase in apoptosis or necrosis could not be detected for etodolac compared with naproxen in vitro did not exclude the possibility that a metabolite of etodolac or a serum factor might be necessary to achieve the effect in vivo. To examine this possibility, the percentages of viable, apoptotic, and late apoptotic/necrotic cells were measured by analysis of the binding of FITC annexin V to and the uptake of propidium iodide by isolated mononuclear cells after administration of etodolac to the patient (data not shown). As the lymphocyte count dropped after administration of etodolac, the percentage of apoptotic cells remained the same. These data suggested that etodolac (at standard anti-inflammatory and analgesic concentrations) did not achieve reduction of leukemic lymphocyte count by direct killing but by increasing the clearance of leukemic cells into other compartments.

To directly determine whether etodolac was enhancing the clearance of the patient’s leukemic lymphocytes, a WBC scan was performed in the standard fashion with and without the administration of etodolac. As shown in Figure 2, an increase in the radiolabel appeared in the spleen with the administration of etodolac. No difference was detected in the amount of radiolabel that appeared in the liver.

These data show that at standard anti-inflammatory doses, etodolac reproducibly lowers the lymphocyte count in a patient with B-CLL. Furthermore, data is presented to show that etodolac achieves this action by affecting changes in leukemic cell compartmentalization. Further work should clarify the prevalence of this effect in B-CLL, the molecular mechanisms involved, and whether or not racemic etodolac, one of its chiral isomers, or similar compounds could be useful in B-CLL or other B-cell neoplasms.

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References

To the editor:

Treatment and outcome of infants with acute myeloid leukemia

We read with interest the article reporting the results of the Japan Infant Leukemia Study Group treatment of infants with acute myeloid leukemia (AML) on the ANLL91 protocol. The event-free survival reported for their patients treated with intensive chemotherapy is quite impressive.1 The authors were very thorough in comparing their results with those of other cooperative groups. Unfortunately, they did not use the most recently published data from the US Children’s Cancer Group (CCG) in their Table 3.1 The updated results of CCG-2891,2 published in January 2001, report the responses of 116 infants treated with allogeneic bone marrow transplant, autologous bone marrow transplant, or chemotherapy alone. Those infants achieved an 8-year actuarial survival of 71%
(allogeneic transplant), 40% (autologous transplant), and 61% (intensive chemotherapy). These numbers are significantly different from the results published in 1996, and compare quite favorably with those reported by Kawasaki et al (72%-74% 3-year survival for a total of 35 patients). While the use of the more recently published CCG results does not change substantively the results or conclusions reached by Kawasaki et al, comparison with the more recent results provides a more appropriate context for evaluating the significance of their findings. These studies complement each other, providing evidence that an age of younger than 1 year is probably not an independent adverse prognostic factor for children with AML, supporting the use of intensive chemotherapy when there is no allogeneic bone marrow donor available.

Rathbun et al have reported apoptosis in the Fanconi anemia (FA) cell line HSC536N in response to interferon-γ (IFN-γ) and agonistic Fas antibodies. While they did not use the classic assays of apoptosis (morphology, TUNEL, DNA laddering), they concluded that cell death was due to apoptosis because of evidence of both caspase 3 and PARP cleavage on Western blots. In order to show cleavage, however, they had to load 100 μg of protein per lane onto the gel and, allowing for overloading, the

To the editor:

Selective serotonin reuptake inhibitors are effective in the treatment of polycythemia vera–associated pruritus

Polycythemia vera is a clonal hematopoietic stem cell disorder characterized by erythropoietin-independent erythrocytosis that is often accompanied by splenomegaly, thrombocytosis, and leukocytosis. The disease is associated with life-threatening thrombohemorrhagic complications and a progressive risk of either transformation to either myelofibrosis with myeloid metaplasia or acute myeloid leukemia. Pruritus, which is often exacerbated by contact with water, occurs in more than 50% of patients with polycythemia vera and may be the most agonizing aspect of the disease, depriving patients of sleep and interfering with their social and physical activities. Phlebotomy with or without cytoreductive therapy, the standard treatment for polycythemia vera, is often ineffective in alleviating disease-associated pruritus. More recently, the use of interferon alpha as a cytoreductive agent in polycythemia vera has proven particularly effective in controlling pruritus. However, cytoreductive treatment in polycythemia vera is generally reserved for high-risk patients, and the antipruritic benefit of interferon alpha is undermined by the well-known side effects of the drug. On the other hand, symptomatic treatment with antihistamines is often ineffective.

On the basis of a serendipitous anecdotal observation as well as reports of efficacy in pruritus associated with advanced cancer, 10 patients (median age, 68 years; 3 female) with polycythemia vera–associated intractable pruritus were treated with selective serotonin reuptake inhibitors. Nine patients received paroxetine (20 mg/d) and 1 received fluoxetine (10 mg/d). All 10 patients had a favorable initial response, which included complete or near-complete resolution of pruritus in 8 patients (80%). Response to treatment occurred within 48 hours in most patients. Two patients have discontinued treatment because of either side effects or leukemic transformation. One of these 2 patients had a partial relapse (loss of “best” response but severity of pruritus still better than baseline) of her pruritus before discontinuing treatment with paroxetine. Eight patients are still on treatment for a period of 1 to 12 months. Among these patients, 3 have experienced side effects including delayed ejaculation, decreased libido, and fatigue. Only 1 patient has had a partial relapse in pruritus.

The current report suggests that a selective serotonin reuptake inhibitor may be considered as a therapeutic option in polycythemia vera–associated pruritus. A prospective, controlled treatment trial that is accompanied by laboratory correlative studies is required to validate the current preliminary observations as well as clarify the mechanism of action.

To the editor:

The Fanconi anemia cell line HSC536N is not sensitive to interferon-γ and does not cleave PARP in response to Fas-mediated cell killing

Kawasaki et al have reported apoptosis in the Fanconi anemia (FA) cell line HSC536N in response to interferon-γ (IFN-γ) and agonistic Fas antibodies. While they did not use the classic assays of apoptosis (morphology, TUNEL, DNA laddering), they concluded that cell death was due to apoptosis because of evidence of both caspase 3 and PARP cleavage on Western blots. In order to show cleavage, however, they had to load 100 μg of protein per lane onto the gel and, allowing for overloading, the

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