as of contamination by peripheral blood leukocytes known to express all major TCRs. Response to immunosuppressive protocols is not always achievable or long-lasting. If clonal T cell proliferation is refractory to this treatment, the use of chemotherapy may be justified.

Key words
Pure red cell aplasia, lymphocytosis, polyglandular syndrome

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Fatal myelofibrosis following fludarabine administration in a patient with indolent lymphoma

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We report a case of fulminant myelofibrosis after administration of fludarabine in a patient diagnosed as having refractory low-grade lymphoma, progressing fatally. Myelofibrosis in the setting of an indolent lymphoma is very rare; this fact, and the short period between drug administration and fibrosis suggest an etiopathogenic link, although this potential and severe adverse effect of fludarabine has not been previously reported in the literature.

Fludarabine is a purine analog which has remarkable activity in several lymphoproliferative disorders, including chronic lymphocytic leukemia and low-grade non-Hodgkin's lymphoma (NHL). Its administration carries some side effects, usually mild or moderate and reversible. Non-hematologic toxicity includes nausea, vomiting, diarrhea, fatigue and neurologic or pulmonary complications. However, the major toxicity reported has been infection related to both myelosuppression and immunosuppression.[1] Uncommon adverse effects are immune disease and bone marrow necrosis.[2,3]

We report the first case, to our knowledge, of fulminant myelofibrosis after administration of fludarabine in a patient with low-grade NHL.

A 62-year-old male with a diagnosis of follicular NHL (grade II, REAL classification) in 1988, was treated with chlorambucil achieving partial response. In October 1995 he was admitted because of tenderness over the lumbar region, night sweats and weight loss. Physical examination was unremarkable, except for an enlarged left cervical lymph node. Peripheral blood count showed Hb: 9.4 g/dL, WBC: 9×10^9/L (normal differential counting) and platelet count: 211×10^9/L. The erythrocyte sedimentation rate was 85 mm in the first hour. Renal and liver function were normal. Lactate dehydrogenase (LDH): 519 IU/L (normal< 480 IU/L), β_2-microglobulin: 2.8 mg/L (normal < 2.4 mg/L). Bone marrow biopsy showed no lymphomatous infiltration. Chest and abdominal tomography (CT) revealed splenomegaly, retroperitoneal adenopathy and enhanced density of two lumbar vertebrae (L_3, L_4). Combination chemotherapy was started (CHOP) and continued until May 1996, achieving resolution of B symptoms and shrinkage of lymph nodes and spleen. The bone marrow remained without neoplastic infiltration. In July 1996 the patient was admitted with severe weakness, night sweats and fever. Cervical adenopathy was present. The hemoglobin was 7.7 g/dL, WBC 7.9×10^9/L (normal differential counting) and platelet count 278×10^9/L. Fludarabine was started (25 mg/m^2 daily for 5 days). After the second course of fludarabine, peripheral blood count showed pancytopenia (Hb 4 g/dL, WBC 1.6×10^9/L, platelets 15×10^9/L), LDH: 590 IU/L, alkaline phosphatase: 335 IU/L (normal < 250 IU/L). A bone marrow biopsy was performed which showed diffusse fibrotic and sclerotic reactions, and foci of large polymorphic Sternberg-like cells. Despite receiving granulocyte colony-

stimulating factor, blood and platelet support, and empiric antibiotic treatment, the patient died of pneumonia in September 1996.

No specific association is known between primary myelofibrosis and lymphoma, despite a few reported cases of myelofibrosis complicated by concomitant[4] or subsequent lymphoma.[5-7] On the other hand, lymphoma is a recognized, albeit uncommon, cause of myelofibrosis.[6] Severe myelofibrosis in the setting of follicular NHL is exceedingly rare, and its occurrence following fludarabine administration suggests an etiopathogenic link. The role that fludarabine played in our patient's myelofibrosis can only be speculated, but given the short experience with this drug we alert physicians to be aware of this potential severe complication of purine analog administration.

Key words

Myelofibrosis, fludarabine, indolent lymphoma

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In vitro modulation of bcl-2 protein expression, drug-induced apoptosis and cytotoxicity by interleukin-10 in chronic lymphocytic leukemia

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Interleukin-10 failed to modify either the percentage of bcl-2$^+$ cells or the number of bcl-2 molecules, or to reduce 2-chlorodeoxyadenosine- and fludarabine-induced apoptosis. The cytokine at 0.1 ng/mL induced an increase of cell survival both in the absence or in the presence of 2-chlorodeoxyadenosine, while no difference was appreciated with fludarabine.

Controversial results have been recently reported on interleukin-10 (IL-10) as an apoptosis inducer in chronic lymphocytic leukemia (CLL) cells.[1-3] In this regard, we would like to report our experience on its effect on 22 previously untreated CLL patients.

IL-10 (Schering-Plough, Milan, Italy) at 0.1 ng/mL induced a statistically significant increase of cell survival, as measured by the MTT assay,[4] compared to cytokine-free cultures (p=0.024). Similarly, IL-10 0.1 ng/mL significantly raised the 2-chlorodeoxyadenosine- (2-CDA) (Leustatin, Ortho Biotech, USA) LD_{50} values (p=0.009), while no significant difference was appreciated in the fludarabine (FAMP) (Fludara, Schering AR, Germany) group (Figure 1A). IL-10 also failed to reduce significantly the percentage of either 2-CDA- or FAMP-induced apoptotic nuclei (Figure 1B) as evaluated by flow-cytometry analysis.[5] Finally, the percentage of bcl-2$^+$ cells, which significantly reduced after a 4 days of culture, remained unmodified in the presence of IL-10 (Figure 2A). In 11 cases, the number of bcl-2 molecules was also analyzed by DAKO QUIFIKIT assay (Figure 2B). The number of bcl-2 molecules decreased spontaneously after 4 days of culture (14,746 versus 6,689 ABC units, p=0.0044). We failed to document that IL-10 had an effect on reducing bcl-2 antigen density (6,689 versus 6,130 ABC units, p=not significant).

Our data are in line with the results of Jurlander *et al.*[3] regarding the effect of IL-10 in modulating both cell viability and apoptosis of CLL cells. Our experiments, like those performed by Jurlander, were carried out on freshly isolated cells; this is a key point to explain why our and Jurlander results differ from those of Fluckiger.[1] It is worth noting that other authors demonstrated that IL-10 prevents CLL cells from undergoing apoptosis.[2] In our study *in vitro* culture of CLL cells significantly reduced both the percentage of cells expressing the bcl-2 protein content and the antigen density. The addition of IL-10, which has been claimed to down-regulate the bcl-2 product in CLL,[1] slightly, but not significantly, lowered both the percentage and the amount of molecules of the bcl-2 positive-cells. Likewise, a more recent report showed that IL-10 enhanced the survival of CLL cells by inhibiting the process of apoptotic cell death, without increasing bcl-2 expression.[2] The finding that IL-10 mRNA expression is firmly associated with non-progressive disease[6] gives a speculative indication for immunotherapy with rh-IL-10 in CLL patients to prevent disease progression. On the other hand, the fact that the growth of the B-1 malignancy, a murine counterpart of CLL, is dependent on autocrine production of IL-

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