Table 1.

Diagnosis	Number of cases	Response to As_2O_3	Response to +GM-CSF
RAEB-t	3	2/3	ND
AML-MDS	8	5/8	4/8
AML-M3	1	1/1	ND
AML-M0	1	0/1	0/1
CMML	1	0/1	1/1

As_2O_3 24 hours after exposing the cells to GM-CSF. In 5/8 cases the addition of GM-CSF made the cells more sensitive to the apoptotic effects of As_2O_3, particularly at concentrations as low as those known to be effective *in vivo*. Representative experiments are shown in Figure 1.

Two interesting observations can be drawn from our data. The initial levels of apoptosis in our experiments are strikingly similar to those observed in vivo (14% vs 10-15% in ref. #2). Moreover, a relevant proportion of cells from advanced MDS cases seem to respond in vitro to the anti-apoptotic effect of HGF. The role played by the process of cell death in the pathogenesis of MDS is still a matter of debate.[4] We show here that a combination of a pro-apoptotic agent with a differentiative stimulus seems to be able to overcome the relative resistance to apoptosis documented in advanced MDS cases.

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Epoch-cyclosporin A induces high response rates in relapsed lymphomas

We describe the results concerning tolerance, response and survival of a program of rescue therapy for primary refractory and relapsed lymphoma combining cyclophosphamide and prednisone with a 96-hour infusion of etoposide, vincristine, and doxorubicin (EPOCH) with cyclosporin A (CsA).

Sir,

The prognosis of patients with refractory or relapsed lymphoma is very poor in spite of aggressive salvage treatments.[1] Multiple molecular mechanisms involved in drug resistance have been elucidated.[2] It is possible to circumvent some of them by using specific modulators.[3-5] Cyclosporin A can effectively modulate multidrug resistance mediated by P-glycoprotein[4] and other mechanisms.[6] Otherwise, the administration of chemotherapeutic agents as a continuous infusion can circumvent the resistance of patients treated with the same drugs administered in bolus.[7]

In August 1994, we began a program of rescue therapy combining EPOCH infusional chemotherapy[7] with CsA. An intravenous (i.v.) loading dose of CsA 5 mg/kg was given over 2 hours on day 1, followed by 16 mg/kg/d as i.v.-continuous infusion on days 1 to 4. Simultaneously with the CsA continuous infusion of etoposide, vincristine, and doxorubicin were all administered on days 1 though 4. Finally, cyclophosphamide (i.v. bolus on day 6) and prednisone (orally on days 1 through 6) were given. Treatments were repeated every 4 weeks. When possible, patients achieving a response with CsA+EPOCH chemotherapy were consolidated either with high dose chemotherapy and/or radiotherapy.

The characteristics of the 13 patients treated in this way are shown in Table 1.

A total of 51 cycles of CsA+EPOCH were administered. The median number of treatment cycles per patient was two, the range 1-15. Five patients (38%) experienced grade IV leukopenia. Infectious episodes occurred in three patients, and two patients died from these. Other mild toxic events, such as grade II mucositis, fluid retention, hyperbilirubinaemia, pain and central nervous system toxicity were frequently observed. Dose adjustments were required in 6 patients (46%).

The CsA steady-state concentrations showed a high interpatient variability (median 2,117 ng/mL, range 902-2,906). As CsA delays the clearance of some chemotherapeutic agents resulting in enhanced serum drug levels,[8,9] a forty-percent dose reduction with respect to the original EPOCH (without CsA)[7] was initially employed to compensate for this pharmacokinetic interaction and led to a feasible schedule.

There were six objective remissions (46%; 95% C.I.: 19 to 75%): one partial and five complete remissions. The durations of the response were 6 months for the partial and 5, 8, 8, 14, and 34+ months for the complete ones. No responses were seen in the six patients who had failed to achieve a response with their pri-

Table 1. Patient Characteristics.

Characteristic	*No.*	*%*	*Range*
Total no. of patients	13	100	
Sex			
male	6	46	
female	7	54	
Histology			
Diffuse large B-cell	7	54	
B-cell small lymphocytic*	2	15	
Peripheral large T-cell	2	15	
Angioimmunoblastic T-cell	1	8	
Anaplastic large-cell CD30+	1	8	
IPI at diagnosis†			
low or low-intermediate	7	54	
high-intermediate or high	6	38	
IPI at CsA+EPOCH initiation			
low or low-int	5	38	
high-int or high	8	54	
Type of recurrence			
Primary refractory	6	46	
First relapse	6	46	
Second relapse	1	8	
Previous therapies received			
Conventional chemotherapy			
median no. of regimens	2		1-6
median no. of drugs#	11		8-13
median no. of cycles	8		2-27
High dose chemotherapy			
no	8	62	
yes	5	38	
Radiotherapy			
no	7	54	
yes	6	46	

**Histologic progression was present in both cases at the initiation of CsA+EPOCH. †IPI: International Prognostic Index. #Different corticosteroids are considered as one drug.*

mary chemotherapy regimen. The remission rate in patients with a relapse from a complete remission was six out of seven (86% ; 95% C.I.: 42.1 to 99.6%). Of interest, five of them had previously received high dose chemotherapy treatment as they had had high risk lymphomas at the time of diagnosis. Actuarial survival was 18%, median survival was 7 months (95% C.I.: 0.5 to 13) and event-free survival was 8%. Patients with primary refractory lymphoma had significantly worse overall survival than patients in relapse (median survival 2.3 vs 11.3 months; p=0.01).

In conclusion, this novel approach combines two different strategies to overcome multidrug resistance. In this pilot study, CsA+EPOCH obtained high response rates in patients with heavily pretreated relapsed lymphomas. However, we found no responses in patients with primary refractory lymphoma, suggesting that the resistance found in these tumors involves different resistance mechanisms.[2] A better understanding of these mechanisms is necessary to design treatments which will be able to overcome multidrug resistance and to improve the survival in patients with refractory lymphoma.

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Subacute spinal cord infarction due to zygomycotic thrombosis in a patient with myelodysplastic syndrome

A 58-year old man with myelodysplastic syndrome developed subacute-onset myelopathy, which did not respond to local irradiation. He finally died of pneumonia. The post-mortem examination revealed disseminated zygomycosis in the lung and the spinal vasculature, causing transverse spinal infarction. Disseminated zygomycosis can be responsible for myelopathy in patients with a hematologic malignancy.

Sir,

Myelopathy is rare complication in patients with a hematologic malignancy. Leukemic infiltration, infection, hemorrhages and cytotoxic agents can be responsible for this complication.[1] We recently cared for a patient who developed myelopathy caused by