Cyclosporine Treatment of Refractory T-Cell Lymphomas

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Background. **Cyclosporine (cyclosporin A, CSA) prolongs the survival of transplanted organs by reducing the transcription of cytokines, especially interleukin-2, that are thought to mediate T-cell expansion and subsequent graft rejection. Recently, CSA has been suggested as a potentially effective agent in the treatment of T-cell neoplasms. As a result, a Phase II trial of CSA was done in patients with refractory T-cell lymphomas.**

Methods. **Patients with peripheral T-cell lymphoma (PTCL) or cutaneous T-cell lymphoma (CTCL) who had disease progression after at least one previous therapy were eligible for participation. CSA was administered orally at a dose of 7.5 mg/kg twice daily, and the patients were followed for disease response and toxicity.**

Results. **A total of 16 patients were treated. Five patients had PTCL, and 11 had CTCL. Most patients were pretreated extensively with chemotherapy and/or radiation therapy. No responses occurred in patients with PTCL. Two of 11 patients with CTCL responded to therapy. Both patients who responded to CSA had recurrent disease that approached baseline levels within 1 week of discontinuing therapy. A second response occurred in both patients after reinstitution of therapy. Although most patients were removed from the study because of disease progression, renal toxicity was significant.**

Conclusions. **Most patients with refractory T-cell lymphomas did not respond to CSA, suggesting that these malignancies are not interleukin-2 dependent or, alternatively, that CSA did not reach its intracellular target. In the two responding patients, the pattern of repeated rapid regression of disease after CSA administration and subsequent rapid recurrence after a temporary halt in therapy suggested that CSA was cytostatic rather than cytocidal or that the clinical remissions were mediated by the antiinflammatory effects of the drug.** ***Cancer*** **1993; 71:2335–41.**

Key words: T-lymphocytes, cutaneous T-cell lymphoma, peripheral T-cell lymphoma, mycosis fungoides, cyclosporine.

The introduction into clinical practice of the fungal metabolite cyclosporine (cyclosporin A, CSA) in 1983 generally is considered the beginning of the modern era of transplantation. One major advantage of CSA over immunosuppressive regimens using cytotoxic agents is its specific interference with T-cell expansion after antigen recognition. Thus, it inhibits rejection without causing significant myelosuppression.[1] The absence of hematopoietic toxicity has been an impetus to the further study of CSA in a variety of unrelated "immune"[2,3] and other poorly understood diseases.[4,5]

Although incompletely characterized, the immunosuppression observed with CSA is thought to be the result of an inhibition of transcription of cytokines, especially the helper T-cell growth factor, interleukin-2 (IL-2).[6–8] At moderate to high concentrations, CSA does not appear to be toxic to either B-cells[9,10] or T-cells with a suppressor phenotype.[11] Continued activity of suppressor T-cells has been postulated to result in a state of tolerance and graft survival.[12]

Currently, there is not uniform agreement regarding the mechanism by which CSA inhibits cytokine transcription and clonal T-cell expansion. However, evidence suggests that the immunosuppressive properties of CSA are mediated by the cytoplasmic protein cyclophilin,[13] which recently has been found to be identical to the enzyme peptidyl-prolyl cis-trans isomerase.[14,15] It has been hypothesized that the complex of CSA and cyclophilin interferes with the expression or activity of DNA binding proteins that are involved in the transcription of early T-cell activation genes.[16,17]

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The effects of CSA on T-cell activation and expansion have led to an interest in the use of this agent for the treatment of T-cell malignancies. One group found that T-cell lymphoblasts from a patient with acute leukemia contained more than twice the CSA binding activity compared with those from other hematologic malignancies.[18] Another study showed that concentrations of CSA that were toxic to T-cell lymphoblastic leukemia cell lines were not toxic to B-cell lines and nonmalignant cells.[19] Similarly, it was reported that the growth of a human T-cell line that constitutively expressed IL-2 and cell surface receptors for IL-2 was inhibited by CSA and that treatment with additional exogenous IL-2 restored normal cellular proliferation.[20]

After noticing the nearly identical surface phenotype of Sézary cells with normal helper T-cells that were inhibited by CSA, one group tested the effect of CSA on cellular proliferation and IL-2 production in lymphocytes isolated from patients with Sézary syndrome.[21] They found that the patient's lymphocytes resembled normal lymphocytes with respect to their capacity to proliferate and secrete IL-2 in response to a combination of phytohemagglutin and phorbol ester. Similarly, these functions were inhibited but not abolished by CSA in both cell types. These authors suggested that CSA might be useful in the treatment of patients with Sézary syndrome.

Based on these studies and a series of case reports[22–27] showing the effects of CSA in patients with cutaneous T-cell lymphoma (CTCL), we did a Phase II clinical trial of CSA in patients with refractory T-cell lymphomas.

Materials and Methods

Patient Eligibility

Our patients were required to have histologic and immunologic marker analysis consistent with T-cell lymphoma and must have had disease progression after at least one standard form of therapy. The eligible tumor types were CTCL (including Sézary syndrome) and peripheral T-cell lymphoma (PTCL). All patients had (1) measurable disease (enlarged lymph nodes by physical examination or computed tomographic scan) or cutaneous lesions documented by clinical photographs and (2) an Eastern Cooperative Oncology Group performance status of 2 or less with adequate renal (creatinine clearance, $\geq$ 60 ml/min; creatinine level, $\leq$ 1.5) and liver (bilirubin, $\leq$ 3.0 mg/dl) function. Staging was done according to the Ann Arbor Staging Classification[28] for patients with PTCL and by the tumor–node–metastasis system for patients with CTCL.[29] Patients taking medication for hypertension were eligible if their blood pressure was 160/100 or less.

Treatment Plan

CSA (provided by Sandoz Pharmaceuticals Corp., East Hanover, NJ) was given to fasting patients at a starting dose of 7.5 mg/kg ideal body weight twice daily (total, 15 mg/kg/day). Verbal instructions on the proper oral administration of CSA were supplemented with written instructions. Physical examinations were done every 2 weeks. Blood urea nitrogen and creatinine levels were measured weekly, and complete blood counts, platelet levels, liver function tests, and lactate dehydrogenase levels were measured every 2 weeks. Direct tumor measurements to monitor disease response (i.e., computed tomographic scans, radiography, or photographs of the skin) were made 6 weeks after beginning therapy or sooner in the event of disease progression. Response and toxicity were graded according to the National Cancer Institute common toxicity guidelines.

Reductions in dose were made as follows: (1) serum creatinine elevation, 2.0–2.9 (25% reduction); 3.0–4.9 (50% reduction); 6.0 or more (hold CSA until creatinine level, < 2.0); (2) bilirubin level, more than 3.0 mg/dl (25% reduction); and (3) blood pressure, 160/100 or more but less than 180/110 (50% reduction) or more than 180/110 (discontinue CSA). In the event of central nervous system toxicity (ataxia, tremors, or seizures), CSA was discontinued, and the patients were evaluated for opportunistic infections. When the symptoms cleared, CSA was restarted at 75% of the initial dose. If the symptoms returned, CSA again was discontinued and eventually restarted at 50% of the dose. After a second recurrence, the patient was removed from the study.

Complete responses were defined as disappearance of all clinical evidence of active tumor for a minimum of 4 weeks. Partial responses were defined as 50% or greater decreases in the sum of the products of all diameters of measured lesions. A reduction in tumor size had to last at least 4 weeks. In patients with skin disease only, the assessment of response was made jointly by the dermatologist and oncologist who were treating the patient. Toxicity were graded according to National Cancer Institute common toxicity guidelines.

Statistical Considerations

In this heavily pretreated group of patients, a 30% response rate was considered appropriate for further investigation. If none of the first nine patients responded to therapy, the study would be terminated with greater than 95% confidence that the true response rate was

less than 30%. If one or more responses were observed, an additional 16 patients would be enrolled. A total of 25 patients entered in the study would ensure that the estimated standard error associated with the observed response rate was 0.10 or less. All patients entered were considered eligible for analysis.

Results

Seventeen patients were entered into the study. One patient was declared ineligible after a pathologic review. The remaining 16 patients were treated and evaluable for their responses and toxicity. The pretreatment disease characteristics, prior therapy, response, and duration of therapy are outlined in Table 1. Five patients had PTCL, and 11 had advanced CTCL. No patient had evidence of Sézary cells using routine Wright-stained peripheral blood smears. Twelve of 16 patients had been treated previously with more than one chemotherapeutic regimen. Patient 3, who was not in a high-risk group, eventually was found to have human immunodeficiency virus antibody titers. The duration of CSA therapy ranged from 1 week to 13 months, but only three patients remained in the study for more than 4 weeks.

Despite the brief duration of therapy, the toxicity was significant. Six patients had a moderate to severe decline in renal function, including two patients who were admitted with acute renal failure. One patient had evidence of renal tubular acidosis with hyperkalemia and a creatinine level of 5.5 mg/dl. The second had severe hypertension (190/110) associated with a bitemporal headache. Two patients had infections (oral candidiasis and *Staphylococcus aureus*-related sepsis), and two patients had significant oral mucosal toxicity (oral ulcers in one patient and ulcers plus gingival hypertrophy in the second). One patient each had Grade 2 or higher gastrointestinal (diarrhea), central nervous

Table 1. Pretreatment Disease Characteristics, Prior Therapy, and Response to Cyclosporine Therapy

Patient no.	Age (yr)	Sex	Disease	Stage	Previous therapy	Response	Duration of cyclosporine therapy	Follow-up
1	65	M	DML	IVB	M-BACOD; cyt/VP/bleo; dox; HN2/ vinblastine; MTX/FH_4; CDDP/ DTIC	PD	2 wk	DOD
2	57	F	CTCL	IV	Total skin electron beam; adj. dox/ cyt; VP; topical HN2; PROMACE; trifluoperezine/bleo	PD	2 wk	DOD
3	44	M	DLCL	IVB	CHOP; MOPP; MTX/FH_4	PD	4 wk	DOD
4	32	M	CTCL	IV	CHOP, PROMACE/MOPP	PD	2 wk	DOD
5	36	F	CTCL	IV	Total skin electron beam; adj. dox/ cyt; topical HN2, PROMACE; deoxycoformycin; isotretinoin; MOPP	PD	4 wk	DOD
6	48	M	CTCL	IV	Total skin electron beam; adj. dox/ ;cyt; topical HN2	CR	13 mo	AWD
7	32	F	CTCL	IV	Topical HN2; dox; cyt/bleo/DTIC; total skin electron beam; VP; isotretinoin	PD	8 wk	DOD
8	57	M	CTCL	IV	Total skin electron beam; adj. dox/ cyt; HN2; isotretinoin	PD	1 wk	DOD
9	56	M	CTCL	IV	Total skin electron beam; PROMACE; dox/cyt/MTX/VP	PD	2 wk	DOD
10	60	M	CTCL	IV	CHOP, PROMACE, FAM, trifluoperazine/bleo	CR	10 wk	AWD
11	55	F	DLCL	IVB	Cyt/dox/VP; ara-C/bleo/MTX/bleo	PD	2 wk	DOD
12	53	M	CTCL	IV	Total skin electron beam; photopheresis	Drug-related death(?)	1 wk	DOD
13	33	F	CTCL	IV	Chloram; total skin electron beam	PD	3 wk	DOD
14	64	M	DLCL	IVB	Local RT; MOPP; cyt/VP/prednisone	PD	3 wk	DOD
15	75	F	DLCL	IVB	Local RT	PD	3 wk	DOD
16	75	F	CTCL	IVB	Total skin electron beam; adj. dox/cyt	PD	3 wk	DOD

DML: diffuse mixed lymphoma; M-BACOD: methotrexate, bleomycin, doxorubicin, vincristine, dexamethasone; HN2: nitrogen mustard; DTIC: dacarbazine; AWD: alive with disease; DLCL: diffuse large cell lymphoma; CTCL: cutaneous T-cell lymphoma; adj: adjuvant; cyt: cyclophosphamide; MTX: methotrexate; FH_4: leucovorin; VP: etoposide; HN2: nitrogen mustard; dox: doxorubicin; bleo: bleomycin; CDDP; cisplatin; Chloram: chlorambucil; FAM: 5-FU, doxorubicin, mitomycin C; PROMACE: prednisone, doxorubicin, methotrexate, cyclophosphamide, etoposide; MOPP: mechlorethamine, vincristine, prednisone, procarbazine; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; RT: radiation therapy; PD: progressive disease; CR: complete response; DOD: dead of disease.

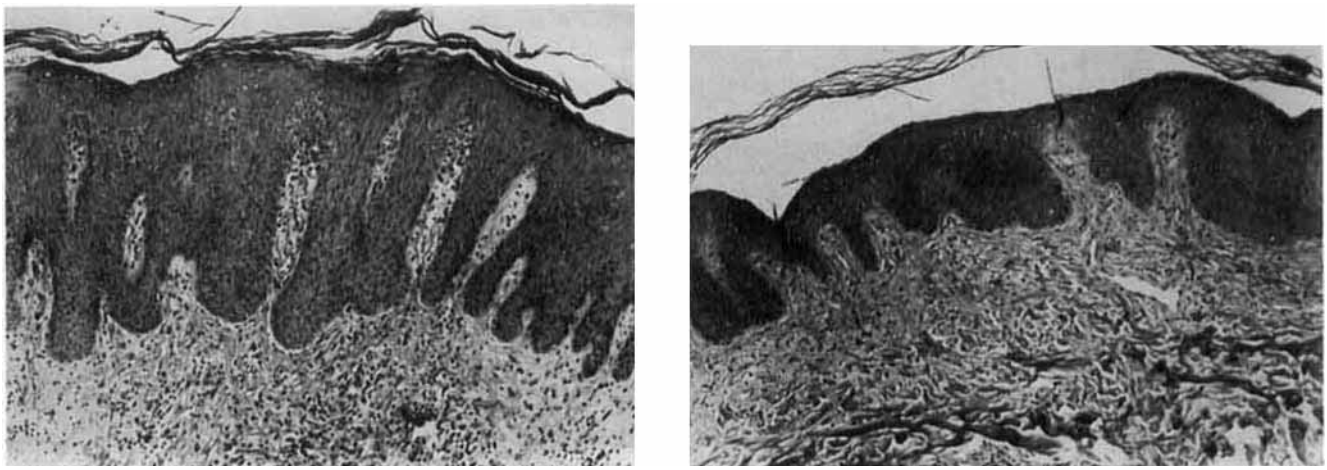

Figure 1. (Left) Hyperkeratosis, focal loss of granular layer, psoriasiform hyperplasia of the epidermis, and lymphocytic infiltrate of papillary dermis with exocytosis of lymphocytes into the epidermis (original magnification ×150). (Right) Significant decrease in epidermal hyperplasia and lymphocytic infiltrate and return of the stratum corneum and granular layer to normal (original magnification ×150).

system (painful peripheral neuropathy), hematologic (anemia), and cardiac (supraventricular tachycardia) toxicity. All toxicities rapidly resolved after a reduction in the dose of CSA or a discontinuation of therapy. One possible drug-related death was seen in a patient who was receiving the oral hypoglycemic agent glyburide. After 1 week of therapy, the patient became stuporous and died of complications attributed to hypoglycemia. Postmortem examination revealed a massive involvement of the liver by lymphoma.

Two of 16 patients responded to therapy (12.5%; 95% confidence interval, 4–35%). None of five patients with PTCL responded to therapy. Both clinical complete responses occurred in patients with near-total CTCL skin involvement. In both patients, skin biopsy specimens after CSA therapy was begun showed a dramatic reduction in epidermal and dermal lymphocytic infiltration (Figs. 1 and 2) compared with prestudy samples. Both patients with clinical complete responses required a dose reduction of CSA, and intermittently, therapy was discontinued because of renal insufficiency. In both patients, disease activity approached their baseline values within 1 week after therapy was discontinued, and a major response occurred again after the readministration of CSA at a lower dose. One patient eventually became resistant to CSA despite a measured whole blood concentration 10-fold higher than at the time of his initial response. The second patient who had a clinical complete response had therapy discontinued because of severe renal insufficiency. At the time therapy was withdrawn, disease activity was present, suggesting the development of drug resistance. In both patients, exfoliative erythroderma occurred after cessation of therapy, but it was controlled well with open wet dressings or corticosteroid administration.

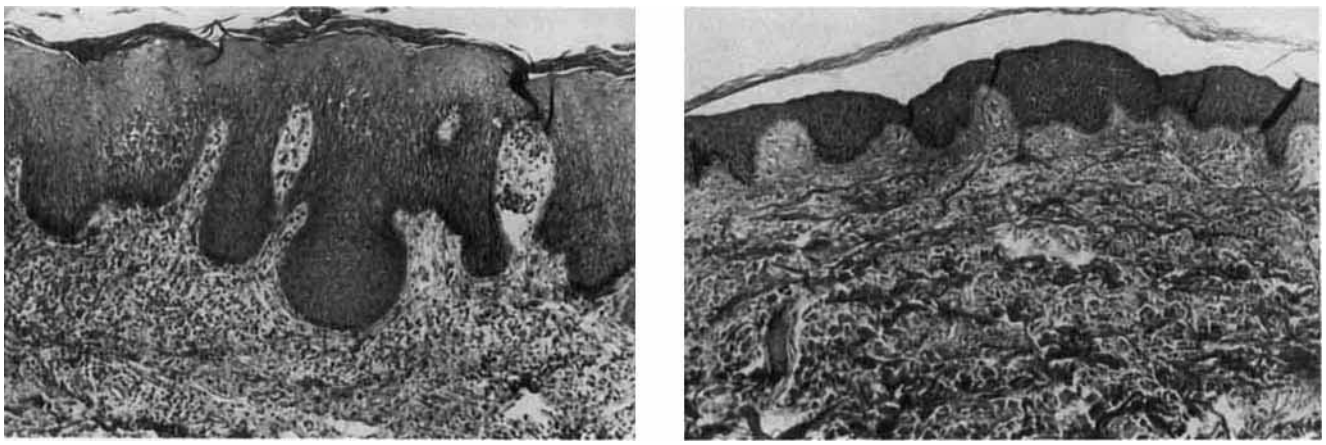

Figure 2. (Left) Hyperkeratosis and parakeratosis, irregular hyperplasia of epidermis, and band-like infiltrate of lymphocytes in papillary dermis with focal exocytosis (original magnification ×150). (Right) Marked decrease in epidermal hyperplasia and lymphocytic infiltrate with return of stratum corneum and granular layer to normal (original magnification 150×).

Blood concentrations of CSA were measured by high-performance liquid chromatography in six patients, and they were highly variable between patients and within the same patient. The levels ranged from 18 ng/ml (in the patient with documented diffuse intestinal involvement) to 600 ng/ml (mean, 293 ng/ml) while the initial dose was being administered. Patient 6 had a clinical response at a time when the CSA level was 22 ng/ml. At the time of relapse, the CSA concentration was 264 ng/ml.

Discussion

Both in vitro studies[19–21] and clinical case reports have suggested a potential role for CSA in the treatment of refractory CTCL[22–27] and other lymphoid malignancies.[30,31] It has been suggested that remissions of unusual clinical syndromes after treatment with CSA represent circumstantial evidence that T-cells were involved in the cause of the underlying disease.[32] However, when one group recently reviewed their experience in five patients with CTCL, it was found that, although inflammatory-type symptoms (such as pruritus and erythema) often temporarily responded to therapy, objective durable tumor responses were not observed.[33] In addition, to our knowledge, there have been no reports of the activity of CSA in patients with PTCL. Thus, the goal of this Phase II trial was to determine the activity of CSA in refractory T-cell malignancies.

In the current study, 2 of 11 patients with CTCL and 0 of 5 patients with PTCL responded to CSA (overall response rate, 12.5%; 95% confidence interval, 4–35%). Because of significant drug-related toxicity, it is unlikely that higher daily doses of CSA could have been administered. The dose we used was the same or higher than that used in previously published case reports. Neither is it likely that a lower daily dose of CSA over a longer period would have been more effective because 15 of 16 patients were removed from the study after disease progression. The other patient was removed from study because of drug toxicity, but clinically, recurrent disease was present. Because of the apparent low response rate and drug toxicity, the study was terminated before treating 25 patients.

There were no obvious differences in the extent of skin involvement or the intensity of previous therapy in the two patients with CTCL who responded to therapy versus the 11 patients who did not respond. A pattern of dramatic regression after CSA administration and subsequent rapid recurrence after drug withdrawal was observed repeatedly in both patients. This would suggest that CSA exerted a cytostatic rather than a cytotoxic effect, or alternatively, CSA therapy resulted in clinical improvement by abrogating an inflammatory response secondary to the tumor cells. Thus, after cessation of therapy, both patients had an exfoliative erythroderma, which subsequently was controlled with topical therapy or systemic steroids. Patient 6 subsequently had pustular psoriasis; both patients underwent skin biopsies before therapy that showed marked psoriasiform epidermal hyperplasia. It is interesting that CSA has been shown to be highly effective in patients with psoriasis,[5] and although its mechanism of action has not been established, a disruption of the epidermal cytokine network has been postulated.[34]

The mechanism of resistance to CSA in unresponsive patients is unknown. However, because lymphoma specimens from most patients with PTCL and CTCL do not express IL-2 receptors on their cell surfaces,[35] it seems likely that these neoplasms are not dependent on IL-2 and, therefore, are unlikely to respond to CSA. Similarly, it would be predicted that other therapies directed at the IL-2 receptor would be successful in a low percentage of patients. At the time of this study, the measurement of IL-2 receptors on frozen tissue was not being done routinely, and it would be interesting in future studies to correlate IL-2 receptor expression with response to CSA or other agents with similar activity.

Another possible mechanism of CSA resistance is extrusion of the drug from the intracellular milieu by the multidrug-resistance (*mdr*) gene product, p-glycoprotein.[36] Expression of p-glycoprotein has been found in relapsing leukemias[37] and lymphomas[38] and is a major target of many current treatment protocols in patients with relapsing disease.[39] Recently, we reported preliminary results that showed expression of the *mdr* phenotype in 6 of 12 patients with Sézary syndrome. In four patients with *mdr*-positive cells subsequently treated with combination chemotherapy, none responded to treatment.[40]

CSA, like verapamil, is effective in reversing the increased efflux of drugs from *mdr*-containing tissue culture cells;[41] however, there is conflicting evidence regarding the way in which CSA itself is handled by multidrug-resistant cells. One group showed that CSA accumulation was reduced markedly in multidrug-resistant cells.[42] Another found that CSA uptake essentially was identical in drug-resistant and drug-sensitive parental cell lines.[41] Further work is needed to evaluate CSA accumulation in human tumors expressing the *mdr* phenotype.

Summary

Treatment with CSA resulted in two objective clinical responses in 11 patients with CTCL and no objective

responses in 5 patients with peripheral T-cell lymphoma. The dramatic recurrence of disease in the responding patients after an interruption of therapy suggested that either CSA was cytostatic and not cytocidal or that the beneficial effect of CSA was produced by markedly reducing the inflammatory component of CTCL. Although nearly all patients were removed from the study after disease progression, significant renal toxicity is likely to limit further studies of CSA as a single agent. The finding that most lymphomas were resistant to CSA suggests that either IL-2 was not necessary for lymphoma cell division or that accumulation of CSA was reduced, perhaps secondary to the expression of the multidrug-resistance phenotype. However, the dramatic responses observed in two patients with disease refractory to conventional treatments should be an impetus to determine ways to identify patients who might benefit from agents with similar biologic activity to CSA but that have less toxicity.

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