

such as instability of the messengers or alterations of the cell cycle could be taken in account. To conclude, for the first time, a reduced expression of DHFR has been demonstrated in 5q- syndrome erythroblasts by qualitative and quantitative studies. This enzyme abnormality could have an important role in the pathogenesis of the disease.

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Key words

Dihydrofolate reductase, cytophotometric analysis, 5q-syn-
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Beneficial effect of low dose G-CSF and cyclosporin-A in a case of chronic neutropenia

A woman suffering from symptomatic acquired chronic neutropenia with a clonal T-cell expansion did not respond to prednisone, full dose cyclosporin-A (CSA) or G-CSF alone. A clinically relevant response was obtained by combining very low doses of CSA and weekly G-CSF administration.

Sir,

Acquired severe chronic neutropenia is a rare autoimmune disease, often associated with a clonal T-cell expansion.^{1,2} Infectious complications are frequent and can be fatal. At present, there is not a standard therapeutic approach. Only a few drugs have proven to be beneficial, including cyclosporin-A (CSA) and granulocyte colony-stimulating factor (G-CSF).³⁻¹⁰ A 59-year old woman was diagnosed in 1992 as having severe neutropenia possibly of an immunologic cause. Indeed, a CD3/CD8 and DR positive T-cell population, demonstrated in bone marrow by flow cytometry, proved to be clonal by T-cell receptor β chain gene rearrangement (R-TcR). No large granular lymphocyte excess was detected in peripheral blood. The patient received a course of prednisone 1 mg/kg and subsequently full dose CSA for two years, without any effect. G-CSF was then added and the dose of CSA was reduced; the neutrophils count reached $> 3.000/\mu\text{L}$ and the patient's clinical condition improved. Because of supply shortage, the patient interrupted G-CSF administration for 10 weeks: neutrophils fell to less than $1.500/\mu\text{L}$ and a dental abscess appeared. An attempt to lower CSA dose to 25 mg/day was carried out in 1999, but was discontinued because neutrophil count fell below $1.000/\mu\text{L}$. Treatment regimens and follow-up data are summarized in Table 1. At present the patient is alive and well; treatment consists of CSA 50 mg daily and G-CSF $300 \mu\text{g}$ s.c. weekly. Plasma monoclonal CSA is $\cong 30 \text{ ng/mL}$, blood pressure is normal, no side effects are present.

The use of CSA and G-CSF alone or in combination for the treatment of chronic neutropenia has been explored in several studies, which are summarized in Table 2. It appears that our original schedule is the lowest for CSA and among the lowest for G-CSF. Our search for the lowest effective doses of CSA and G-CSF was justified by the need to avoid possible damage related to lifelong immunosuppression and to

Table 1. Treatment regimens and follow-up data of the patient.

	Therapy	N/ μL	Complications/ side effects	Hosp.
Dec 91-Feb 93	None/PDN 75 mg/day	$\leq 1,000$	Sepsis	5
Feb 93-Feb 95	CSA 400 mg/day	$\cong 1,000$	Hypertension, diarrhea	8
Feb 95-Apr 95	None	≤ 250	Sepsis	None
Apr 95-May 98	CSA 50 mg/day + G-CSF 300 μg /week	$\cong 3,000$	None	None
May 98-Jun 98	CSA 50 mg/day	$\cong 1,500$	Sepsis	None
Jul 98-Mar 99	CSA 50 mg/day + G-CSF 300 μg /week	$\cong 3,000$	None	None
Mar 99-Jul 99	CSA 25 mg/day + G-CSF 300 μg /week	$\cong 1,000$	None	None
From Jul 99	CSA 50 mg/day + G-CSF 300 μg /week	$\cong 3,000$	None	None

Hosp.: number of infectious episodes requiring hospitalization. N/ μL : neutrophils/ μL . PDN: prednisone; CSA: cyclosporin A.

Table 2. The use of CSA and G-CSF alone or in combination for the treatment of chronic neutropenia: literature data.

Author (ref)	Pts.	CAD	R-TcR gene		F-up, mo	CS-A mg/day	G or GM-CSF	Neutr. increase
			Diagnosis	F-up				
Thomssen, 1989 (3)	1	No	NR	NR	NR		GM: 4 µg/kg days 1-7; 8 µg/kg days 7-14	NO
Lang, 1992 (4)	1	No	POS	NR	2		G-CSF 960 µg/day; then 300µg/day followed by 300 µg every 3 weeks	YES
Walls, 1992 (5)	1	Yes	POS	NR	7		G-CSF 5 µg/kg/day for 19 days monthly	YES
Cooper, 1993 (6)	1	No	NR	NR	NR		G-CSF 263µg/day; every other day as maintenance	YES
Vickers, 1994 (7)	1	No	POS	NR	18		G-CSF 3-7 µg/kg/weekly	YES
Jackubowski, 1995 (8)	1	No	POS	Neg	36	300, then tapered	G-CSF 20 µg/kg/daily	YES
Stanworth, 1998 (9)	8	Yes	POS 1 NR 7	Red	6*		6 P: G-CSF 263 µg/day 2 P: GM-CSF 300 µg/day	YES: 6/8; 2 pts dropped for side effects
Sood, 1998 (10)	6	Yes	POS	POS	55*	2-3 mg/kg	In 1/8 not responding to CSA: GM 1.5 µg/kg/day	YES
Present report	1	Yes	POS	Neg ^a	63	50	G-CSF 300 µg/ weekly	YES

Pts.: number of patients; CAD: concomitant autoimmune disease; R-TcR gene: documented T cell clone; Diagn: at diagnosis; F-up: during the follow-up; NR: not reported; Red: reduced; *median; ^aa faint band reappeared when CSA was reduced, for a short while, to 25 mg/day.

reduce treatment costs. Each drug given as single agent treatment proved to be ineffective; the beneficial effect exerted by the combination suggests that these drugs may have additive effect in chronic neutropenia, either acting on a single target or on separate pathways. The efficacy of this low-dose regimen needs to be confirmed in other patients with similar disorders.

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