Alkylating cytostatic treatment in renal amyloidosis secondary to rheumatic disease

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SUMMARY Fourteen consecutive patients with chronic inflammatory rheumatic disease and reactive renal amyloidosis were treated with alkylating cytostatics in 22 separate periods varying in duration between six and 30 months. Chlorambucil alone was given in 14 treatment periods, cyclophosphamide alone in six, and both alternately in two. The dosage was adjusted to attain a major suppression of the rheumatic inflammation and a blood lymphocyte level below $1.0 \times 10^9/l$. Renal function improved in 12 treatment periods, renal deterioration was arrested in three periods, and in another four periods the rate of functional decline slowed down. In the remaining three treatment periods, associated with further deterioration in renal function, treatment was inadequate owing to blood dyscrasia and failure to control hypertension. Glomerular filtration rate (GFR) was followed more closely in 10 treatment periods, in all of which the falling trend was arrested or reduced. The survival rate at five years was 93%. Three patients who dropped out of the treatment programme are so far the only ones not still alive. Nine are still being followed up after 6-17 years, and the other two remaining live patients have had renal transplants for five years.

Key words: chlorambucil, cyclophosphamide.

As stated in recent reviews there is still no generally acknowledged treatment for preventing progression of renal reactive amyloidosis, also known as the secondary or AA form.¹⁻³ It often occurs as a result of rheumatic inflammatory disease. When dialysis or transplantation are not applicable, death after a median time of five years has been reported.^{4,5}

Arrest, or even regression, of amyloid deposition has been shown to occur when the underlying inflammatory disease has been eliminated or improved.⁶ Cytostatic agents appear to have the capacity to suppress rheumatic inflammatory processes and thereby the production of the circulating precursor of the AA protein, the acute phase reactant serum amyloid A (SAA) protein. The alkylating cytostatic drugs, cyclophosphamide (Cy) and chlorambucil (Ch), are probably the most powerful in this respect. Ch has been used in juvenile chronic arthritis (JCA) with renal amyloidosis in England, Poland, and West Germany, but the outcome has been recorded in only one report,⁷ in which results were reported to be promising. In another study with follow up biopsy,

regression of renal amyloidosis was found after treatment with Cy.⁸

In the present study 14 patients with rheumatic disease and reactive renal amyloidosis were treated with Cy or Ch, or both, in a total of 22 separate treatment periods. The results suggest an ameliorating effect on the course of the renal process. Experience from several other cases with shorter observation periods appears to corroborate this finding.

Patients and methods

Fourteen consecutive patients with rheumatic disease and renal amyloidosis (Table 1) were treated with Ch or Cy, or both (Table 2). Nine had rheumatoid arthritis, one had JCA, and four had ankylosing spondylitis. The amyloidosis was verified by biopsies (Table 1).

All patients had proteinuria with or without nephrotic syndrome (Table 1), and all but two showed substantially decreased kidney function (Table 2).

Serum creatinine and endogenous creatinine clearance were determined by routine methods, and in most instances the GFR was assessed as ⁵¹Cr-

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Table 1 Clinicopathological data of 14 patients with rheumatic disease and secondary renal amyloidosis

Patient No	Sex	Rheumatic diagnosis	Age at onset	Amyloidosis diagnosed after years	Amyloidosis in biopsy		Clinical picture at amyloidosis diagnosis
					Site	Immunofluorescence glomeruli	
1	F	RA	19	13	Kidney	NP	NS
2	F	AS	23	12	Skin		NS
3	M	AS	18	11	Kidney	NP	NS
4	F	RA	34	28	Rectum		Proteinuria
5	F	RA	52	7	Rectum		Proteinuria, haematuria glomerulonephritis, hypertension
6	M	AS	20	8	Kidney	IgG, M, A, C3	NS
7	M	RA	29	20	Kidney	NP	NS
8	M	AS	15	13	Kidney	No glomeruli	Proteinuria
9	F	RA	35	10	Kidney	No glomeruli	NS
10	M	RA	18	19	Kidney	NP	NS
11	F	RA	37	20	Kidney	IgG, M, C1q, C3	NS
12	F	RA	38	19	Kidney	No glomeruli	Proteinuria, hypertension
13	M	JCA	10	22	Kidney	IgG, M	Proteinuria
14	F	RA	38	19	Skin		NS

AS=ankylosing spondylitis; RA=rheumatoid arthritis; JCA=juvenile chronic arthritis; NP=not performed; NS=nephrotic syndrome

EDTA clearance.⁹ Proteinuria was assessed either as g/l or, in most instances, as the albumin clearance expressed as per mille of the creatinine clearance, i.e., $10^3 \times \text{C-alb:C-creat}$ (reference value <0.01). A change of more than 15% was considered significant for GFR or S-creatinine, or both, and of more than 30% for C-alb:C-creat. Available GFR values in seven patients permitted estimation of the average change of function in periods before, during, and after treatment (Fig. 1).

The cytostatic treatment was given for six months or more in a total of 22 separate periods. In the beginning of the 1970s Cy was our first choice, but later Ch was preferred as it is often better tolerated and does not entail hazards to the bladder. In two periods treatment was started with Cy but later switched to Ch. Dosage was adjusted to obtain a peripheral lymphocyte level of less than $1.0 \times 10^9/l$, which in our experience is usually necessary to ensure a substantial reduction of the systemic inflammatory activity.

A 'synovitis index', shown to correlate with laboratory indices of inflammatory activity,¹⁰ was calculated by giving one point for slight swelling and two points for marked swelling (recorded by a rheumatologist, KB or CK), and adding the scores from the following joints: proximal interphalangeal (10 joints), metacarpophalangeal (10 joints), wrist, elbow, knee, ankle, and metatarsophalangeal (counted as one joint for each foot). Since 1980, C reactive protein in serum (CRP) has been assessed as an additional estimate of inflammatory activity (12 periods).

Confidence limits for frequency values were taken from binomial distribution tables. The significance of change from one period to another (Fig. 1) was calculated with Wilcoxon's signed rank test.

Results

In the 22 periods of treatment with alkylating agents the duration exceeded six months in 18 and 12 months in seven (median duration 12). Reduction of lymphocyte levels to near $1 \times 10^9/l$ or below was attained in all but two periods (patient No 2, period 1; and patient No 14). When the synovitis index was 2 or more at the start of treatment (16 periods, 2-3 points, median 12) there was always a reduction (Table 2) at the end of the medication period (0-4 points, median 1). Adequate data were not available in two periods. CRP diminished in 9/12 periods.

In 12 treatment periods renal function improved (I, Table 2). Proteinuria diminished or disappeared in all. Oedema decreased in seven periods, while GFR was stable in 10 and improved in two. A substantial rise of GFR occurred only in period 1 of patient No 6 (Table 2), which may be explained by withdrawal of phenylbutazone or possibly by elimination of renal oedema. CRP was followed in five periods of improvement and found to decrease markedly in all five.

During three periods there was no significant change either in proteinuria or GFR (S, Table 2). In another four periods, the GFR decreased or S-creatinine increased, or both, significantly, but at slower rate than before administration of the

Table 2 Changes in renal and joint variables during 22 periods of cytostatic treatment in secondary amyloidosis

Patient No	Cytostatic therapy	Diuretic therapy F (mg/day)	Values at start and at end of the cytostatic treatment period												Renal process	Survival (years)		
			Oedema (0 to +++)		S-albumin (g/l)		10 ³ ×C-alb: C-creat		S-creatinine (umoll)		GFR (ml/min)		CRP				Synovitis index	
			Start	End	Start	End	Start	End	Start	End	Start	End	Start	End			Start	End
1	Cy	20-0	++	0	24	44	2.98	2.88	50	50	125‡	135‡			8	3	S	
	Cy	40-0	0	+	25	32	6.28	1.48	60	50	135‡	140‡			15	5	I	
	Cy	40-40	0	+	21	35	0.4	0.1	55	55	113	113			31	1	I	
2	Ch	320-160	++	+	13	16	4.3	2.9	50	55	63	57			17	0	I	
	Ch	250-125	+++	0	7	11	24.7	26.6	125	210	27‡	23‡			26	0	P(RF)	
3	Cy	320-40	+++	0	13	34	3.4	0.9	70	75	84	83			13	3	I	
4	Cy	160-40	+	0	26	44	0.9	0.2	75	80	47	45			25	6	P	
5	Cy	120-80	++	+	30	30	0.3	1.5	60	85	74	45			22	3	I	
	Ch	80-80	++	0	30	42	1.5	0.0	95	90	45	40			22	3	I	
6	Cy-Ch	250-40	++	0	22	40	8.8	0.8	170	110	35	62			8	0	I	
	Cy	0-0	0	0	25	33	1.2	1.6	120	100	57	54	17	<12	2	1	S	
7	Ch	250-125	++	0	18	27	9.4	9.4	160	230	40	32	94	45	1	1	P(RF)	
8	Ch	0-0	0	+	34	22	0.6	8.2	140	215	50	32	120	160	7‡	1	P	
9	Ch	160-160	0	+	18	22	9.5	11.9	230	410	16	20	20	12	6	0	P	
10	Ch	80-40	++	+	16	28	1.0	0.8	70	70	89	91	49	14	2	1	I	
	Ch	40-40	0	+	31	18	1.5	3.8	75	89	64	60	16	43	1	2	P(RF)	
	Ch	80-40	++	+	18	35	5.3	1.2	128	151	39	38	69	<12	4	1	I	
11	Ch	80-80	0	0	20	37	0.3	0.0	105	120	40	37	42	<12	1	5	I	
	Ch	80-40	0	0	40	33	0.0	0.0	119	119	32	36	<12	<12	0	2	S	
12	Ch	0-0	0	0	32	34	1.4	0.6	170	180	30	28	52	<12	10	2	I	
13	Ch	60-60	++	0	22	25	0.8	4.8	60	136	76	35	59	33	13	1	P(RF)	
14	Ch	0-0	0	0	22	33	6.1	1.5	154	142	18	30	174	23	3	0	I	

Cy=cyclophosphamide, Ch=chlorambucil, F=furosemide (daily dosage at highest level and at end of observation). Course of renal process: I=improvement, S=stable, P=progress of impairment, P(RF)=progressive but at reduced rate of functional deterioration; C-alb: C-creat=ratio of albumin and creatinine clearance. ‡=stable, †=dead, ‡=kidney transplanted, †=live; ‡=tendogenous creatinine clearance; †=estimated as g/l at stable GFR; ‡=hypertension.

cytostatic drug (P(RF), Table 2); three of these four periods are included in Fig. 1. There was no regular pattern of change in CRP in periods classified as S or P(RF).

In the remaining three periods the rate of deterioration of renal function did not change (P, Table 2). In all of these, treatment was inadequate in some respect. In period 1, patient No 5, there was a moderate hypertension that was insufficiently controlled. In patient No 8, immunosuppression was not attained because of granulocytopenia (up to 14 mg Ch/day). In the third period (patient No 9), hypertension could not be controlled and there was rapid progression to uraemia. Renal angiography showed partial stenosis of the right renal artery.

In the seven cases where $^{51}\text{CrEDTA}$ clearance was determined more frequently (Fig. 1) the GFR increased during three periods of treatment and showed a reduction of decline rate in all of the other seven treatment periods. The median rose from -2.6 to -0.2 ml/min/ 1.73 m 2 /month ($p=0.008$ for $n=7$).

Increase of GFR was never observed when non-steroidal anti-inflammatory drug (NSAID) medication was discontinued, with the possible exception of period 1 of patient No 6 (see above). A significant and persistent fall in GFR followed major surgery in two cases. Hypertension probably contributed to a fall in GFR in three patients, in one of whom (No 10, Table 2) GFR became stable when blood pressure was normalised by heavy anti-hypertensive treatment.

Only one patient, who died of uraemia after 4.5 years, survived less than five years from the detection of amyloidosis (Table 2)—a five year survival rate of 93%. A further two patients died of uraemia one after 5.3 years and the other after 11 years. Two patients (Nos 8 and 9), accounted for survivals of seven and six years respectively, when they received renal transplants, are still alive five years after the operation. Also still alive are nine patients, two of whom have had a total remission of their rheumatic and renal affection for several years. The three patients who died of uraemia had all dropped out of

Fig. 1 Average monthly change in $^{51}\text{CrEDTA}$ clearance before (□), during (■), and after (▨) treatment with cytostatic drugs in 10 periods (patients Nos 3, 6, 7, 10, 11, 13, and 14). The figures below the hatched rectangles (i.e., after treatment) indicate the number of months for which the average change of GFR is calculated. For patient No 13 the period of treatment (Table 2) was 28 months: during the first 12 months the reduction in GFR was 2.7 ml/min/ 1.73 m 2 /month; during the following 16 months the dose of Ch was raised, arthritis and lymphocyte level were more adequately controlled, and the monthly fall in GFR was 0.5 ml/min/ 1.73 m 2 . The treatment was then switched to azathioprine (no 'after Ch' value was calculated).

the treatment programme and lost contact with the department some time before they entered end stage of their renal disease (Table 2). Median survival time is now seven years (range 4.5–17).

None of the patients has so far shown any potentially fatal side effects of the treatment with alkylating agents. Herpes zoster occurred in 4/22 periods, necessitating the interruption of therapy for a couple of months.

Discussion

In the 14 patients followed up the five year survival rate was 93%, significantly more than the 50% ($p < 0.01$) which is characteristic for the natural course of renal amyloidosis secondary to rheumatic disease.^{4,5} The mean survival time is now nine years, a figure that will rise as two patients are in full remission with regard to arthritis and renal affection, and seven patients (i.e., excluding two living with renal transplants) have not yet reached the end stage of renal disease. The three patients who died of uraemia might have lived longer had they continued with the treatment programme.

The unexpectedly favourable trend in survival statistics is corroborated by analysis of the laboratory data (Table 2, Fig. 1). In 15 of the 22 periods of cytostatic therapy, renal function either improved (12 periods) or was stable (three). In another four periods the rate of functional deterioration was slower than before cytostatic treatment. No improvement was obtained in three periods, in all of which there was some inadequacy of treatment. In two of these three periods occurred the only instances of patients (Nos 8 and 9) developing uraemia within a few weeks, despite cytostatic treatment to retard the rate of deterioration of renal function. Specific study of GFR (⁵¹CrEDTA clearance) in 10 periods of treatment also indicated inhibition of renal functional decline (Fig. 1).

As there was no control group it is not known whether our seemingly favourable outcome figures are significantly better than might have been obtained in a comparable group receiving placebo.

How long should treatment continue? Based on our clinical experience our present policy is as follows: in nephrotic syndrome Ch/Cy is usually discontinued when $10^3 \times \text{C-alb} : \text{C-creat}$ has been below 1.0 for six months. Where renal function has deteriorated, Ch/Cy is given until the GFR and S-creatinine have been stable for six to eight months. Prolonged treatment should be avoided during periods of inflammatory inactivity, to reduce the risk of non-lymphocytic leukaemia.^{11–13}

Of other possible precautions against impairment of renal function, the importance of the following

should be stressed: radical treatment, such as the administration of angiotensin converting enzyme inhibitors¹⁴ in the event of any incipient hypertension; the avoidance of major surgery^{7,15,16} whenever possible (studies on how to eliminate this source of risk are under way (G Husby, personal communication)); and the avoidance of NSAIDs—with the possible exception of sulindac.¹⁷ A detailed account of the principles we have adopted for the management of secondary renal amyloidosis is to be published elsewhere.

In conclusion, results from these 14 cases of rheumatic disease show that in most instances (19/22 treatment periods) the course of renal amyloidosis was satisfactory or somewhat improved after treatment with Ch or Cy (Ch being the drug of choice). This is in contrast with the generally poor outcome reported for adult rheumatic patients, and is encouraging enough to justify randomised placebo-control studies of Ch treatment, in which emphasis should be given to examining the effect on the course of renal amyloidosis of suppressing SAA concentrations.¹⁸

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