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ORIGINAL ARTICLE

Programmed initiation of hemodialysis for systemic amyloidosis patients associated with rheumatoid arthritis

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Abstract Reactive amyloidosis is a serious systemic disease in rheumatoid arthritis (RA). Amyloid protein can be deposited in kidneys, heart or gastrointestinal tract leading to organ failure. Renal involvement is a well-known complication in amyloidosis as this may culminate in end-stage renal disease (ESRD). Hemodialysis (HD) is always considered the treatment of choice for such patients; however, the prognosis is usually poor due to a large number of sudden deaths immediately following HD therapy. To circumvent the problem of HD initiation while instituting HD safety, we devised a plan to start HD and compare patient's survival with our previous data. Sixty-three patients were treated with HD. They were categorized according to the initiation of first dialysis. All patients were divided into planned, unplanned and programmed initiation groups. First dialysis that had been initiated as not urgent was considered 'planned' (20 patients). First dialysis that had been performed urgently for life-threatening renal insufficiency was considered 'unplanned' (31 patients). First dialysis that had been initiated as not urgent and according to our dialysis program was considered 'programmed' (12 patients). Survival of these 63 patients from the initiation of HD at 38 days was 75%, at 321 days was 50% and at 1,784 days was 25%. Patients with unplanned initiation of HD showed a significant poor survival compared with those of both planned and programmed initiation. Additionally, patients with planned and programmed initiation of HD showed no significant difference for the patients' survival. Our study demonstrates that patients with amyloidosis have a higher mortality rate. Nevertheless, programmed initiation of HD will improve the prognosis of patients with ESRD. Such possibility needs to be considered in more detail in the future.

Keywords Arthritis-rheumatoid · Reactive amyloidosis · Hemodialysis · Initiation · Program

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Introduction

Rheumatoid arthritis (RA) is not itself a life-threatening disease, but it may cause reactive amyloidosis, which carries the risk of organ failure and death [1, 2]. Reactive amyloidosis is a serious systemic disease, which may arise from long-lasting inflammation, as occurs in RA, with elevated levels of serum amyloid A (SAA) proteins. SAA are insoluble fibrinoid proteins that can be deposited in kidneys, heart or gastrointestinal tract and, consequently, lead to organ failure [3]. The prevalence of amyloidosis in RA is variable. The frequency of amyloidosis in RA has been reported to range from 5 to 13.3% in cases confirmed by biopsy and from 14 to 26% in cases confirmed by autopsy [4–6]. A clinical diagnosis of amyloidosis is usually suspected with the onset of proteinuria, renal insufficiency and diarrhea. The histological diagnosis of reactive

amyloidosis is generally established by lip, renal, rectal, abdominal fat aspiration, and gastrointestinal (GI) biopsy [7–9].

Renal involvement is a well-known complication in amyloidosis with RA. It usually manifests itself as a nephritic syndrome with a variable degree of renal impairment that may progress to end-stage renal disease (ESRD). ESRD is a major cause of death in such disease [10–12]. Hemodialysis (HD) is always considered as the treatment of choice in such patients.

Recently, we described the poor prognosis of these dialysis patients. Poor prognosis in these patients was mainly due to a large number of sudden deaths immediately following HD therapy. Additionally, unplanned initiation was significantly associated with poor survival. Therefore, planned initiation of HD was highly recommended to improve patient's survival [13].

Despite the increase in the number of patients who receive regular dialysis, little is known of the requirements to initiate dialysis treatment in patients with end-stage renal disease (ESRD) and patients associated with renal amyloidosis with RA. We carried out a retrospective analysis of the demographic characteristics, patients' conditions at the time of initiating dialysis and outcome. Additionally, we made plan to start HD and compared patient's survival with our previous data. Twelve patients with ESRD and amyloidosis were treated with HD according to the program (programmed initiation).

Patients and methods

Subjects

A total of 63 patients with ESRD and amyloidosis treated with HD between 1982 and 2006 in Niigata University Hospital were included in the study. Each patient satisfied the 1987 American Society of Rheumatology Criteria for RA [13]; anatomical stage and functional class determined according to the system advocated by Steinbrocker [14]. Previously, we described data collected from fifty-one patients [12]. To take the data into consideration, we designed a program to initiate HD safety (Fig. 1). The following 12 patients with ESRD and amyloidosis were treated with HD according to the program (programmed initiation). We compared clinical data and prognosis among three groups (planned initiation, unplanned initiation and programmed initiation). The study protocol was approved by the institutional review board of Niigata University Medical and Dental Hospital, and the subjects gave informed consent to participate in the study.

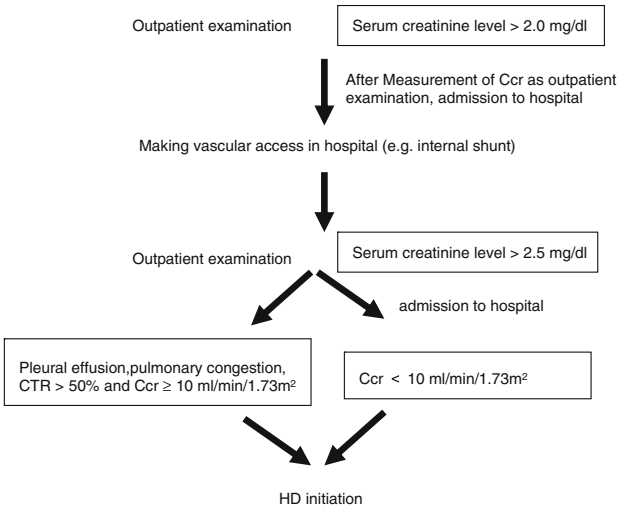

Fig. 1 Program of hemodialysis initiation. Schematic representation of the program of our patients with end-stage renal disease of reactive amyloidosis associated with rheumatoid arthritis. *Ccr* creatinine clearance, *CTR* cardiothoratic ratio

Diagnosis of amyloidosis

Amyloidosis was suspected on clinical grounds. Diagnosis of amyloidosis was confirmed by positive Congo-red staining of renal, rectal, GI and abdominal fat tissues biopsies. Green birefringence was considered as evidence for the presence of amyloid deposits. Potassium permanganate reaction was not performed in these specimens.

Hemodialysis

All patients were treated with HD. They were categorized according to the initiation of first dialysis. All patients were divided into planned, unplanned and programmed initiation groups as follows. First dialysis that had been initiated as not urgent was considered 'planned'. First dialysis that had been performed urgently for life-threatening renal insufficiency was considered 'unplanned'. First dialysis that had been initiated as not urgent and according to our dialysis program (Fig. 1) was considered 'programmed'. We first considered serum Cr levels of 2.0 mg/dl. Our preliminary data revealed that only 1 case out of 39 patients initiated HD under the condition of serum Cr levels of 2.0 mg/dl (data not shown). This was the premise to evaluate serum Cr levels of 2.0 mg/dl when preparing the vascular access of HD. Next, we examined serum Cr levels of 2.5 mg/dl. We previously detected that patients with unplanned initiation of HD started therapy at the state of 2.5 mg/dl of Cr, whereas the equivalent Ccr was about 10 ml/min in patients with amyloidosis [12]. Consequently, we reviewed physical and laboratory examinations and initiated HD. Even if Ccr were over 10 ml/min and pleural effusion,

pulmonary congestion and cardiomegaly were observed in these patients, HD was initiated. None of these patients had been treated with chronic ambulatory peritoneal dialysis (CAPD) or with intermittent peritoneal dialysis.

Statistical analysis

Determination of the onset of the underlying disorder was made retrospectively by reviewing the patient's chart when a diagnosis of amyloid was confirmed. Survival was calculated from the date HD was initiated until the date of death or April 1, 2006, for those patients who remained alive. Standard univariate statistical methods were used to summarize the distribution of each of the variables studied. Survival curves were estimated by the Kaplan–Meier technique. Cox proportional hazard models were used to determine the variables that influenced survival after the initiation of HD. *P* values of less than 0.05 were considered significant, using a two-tailed test.

Results

Clinical features before dialysis

Sixty-three patients with AA amyloidosis associated with RA were evaluated in this study. Nine of the patients were men and 54 were women. All of these patients presented with both symptomatic and asymptomatic signs for amyloidosis. Table 1 shows the clinical characteristics and laboratory findings of these patients at the time diagnosis of amyloidosis and at the time of HD initiation. Low levels of serum albumin were frequent. Inflammatory measures such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated. The differences of clinical characteristics and laboratory findings between the patients with programmed initiation and the other (planned and unplanned) initiation of HD were not significant (data not shown). All amyloid-positive patients were treated with non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs). Post-dialysis treatment data represent the effect of HD.

Dialysis treatment

All the patients were treated with HD. Mean age at initiation of HD was 63.6 ± 9.0 years. Twelve patients were treated with programmed initiation of HD, and the others were treated with planned (20 patients) and unplanned (31 patients) initiation of HD, all of which have been previously described. The Kaplan–Meier survival curve of amyloidosis patients from the initiation of HD is shown in Fig. 2. Survival of these 63 patients from the initiation of HD at 38 days was 75%, at 321 days was 50% and at 1,784 days was 25%. The poor prognosis of patients with RA was mainly due to the large number of early death after the initiation of HD. However, the prognosis of HD patients improved at every point of estimation compared with previous report that we described [12].

Cause of death

By April 2006, 48 patients treated with dialysis had died. The multiple causes of death are shown in Table 2. Heart failure was predominant about half of the deaths, and infection occurred at a frequency of 14.4%. Once these patients succumbed to congestive heart failure, it was difficult for them to recover. Especially, in HD, fluid removal was sometimes difficult to achieve to dry weight, because blood pressure of these patients was unstable and sometimes the hypotension was extensive. Respiratory failure was observed in 3 cases according to the over-hydration, while pancreatitis was observed in 1 case due to gall bladder stone.

Comparing planned, unplanned and programmed initiation of HD

To establish a comparison in the clinical outcome among planned, unplanned and programmed HD, 21 patients received unplanned initiation of HD, 30 patients received planned initiation of HD and 12 patients received programmed HD. As shown in the multivariate Cox analysis, patients with unplanned initiation of HD showed a significant poor survival when compared with those of both unplanned and programmed initiation. Additionally, patients with planned and programmed initiation of HD showed no significant difference in survival (Fig. 2). Because patients with programmed initiation of HD continue to receive therapy, it may be possible to prolong the prognosis in patients with programmed initiation than in patients with unplanned initiation (Fig. 3).

Discussion

Renal involvement is common in amyloidosis and usually manifests itself as a nephrotic syndrome with variable degrees of renal impairment that may lead to ESRD, thus contributing to death of these patients [12]. Due to the systemic nature of the disease, renal replacement therapy is not initially recommended to patients reaching ESRD. Some patients with renal amyloidosis die prematurely of pneumonia, cardiac failure and gastrointestinal bleeding, while others progress to ESRD and require renal replacement therapy, such as HD or continuous ambulatory

Table 1 Clinical characteristics and laboratory findings of 63 amyloid-positive patients with HD

Characteristic			Value
Female sex, *n*(%)			54 (86%)
Mean onset age of RA, yrs (SD) [range]			45.9 (12.0) [20–61]
Mean age of diagnosis of amyloidosis, yrs (SD) [range]			61.1 (9.8) [36–75]
Duration of RA prior to diagnosis of amyloidosis, yrs (SD) [range]			15.7 (9.1) [4–33]
Mean age of initiation of HD, yrs (SD) [range]			63.6 (9.0) [40–76]
Stage, *n* (%)			
I			0 (0%)
II			0 (0%)
III			17 (27.0%)
IV			46 (73.0%)
Class, *n* (%)			
1			0 (0%)
2			30 (47.7%)
3			28 (44.4%)
4			5 (7.9%)
	Mean (SD)%		Criterion
	Before first HD	End of first HD	
Total protein, g/dl	5.4 (0.9)	ND	6.6–8.0
Serum albumin, g/dl	3.0 (0.8)	ND	4.1–5.0
Hemoglobin, g/dl	8.4 (2.1)	ND	10.7–14.8
Hematocrit,%	24.7 (6.2)	ND	32.8–50.8
BUN, mg/dl	72.9 (32.3)	32.4 (19.2)	8–20
Cre, mg/dl	4.6 (2.7)	2.5 (1.4)	0.5–1.1
UA, mg/dl	7.8 (2.5)	3.6 (2.5)	2.9–7.5
HCO_3^-, mMol/l	20.2 (5.0)	ND	23.0–26.3
Ccr, ml/min	8.3 (5.4)	ND	<80
CRP, mg/dl	4.1 (4.6)	ND	<0.3
ESR,mm/h	79.7 (46.8)	ND	<15
RF, IU/ml	69.2 (115.3)	ND	<10
IgG, mg/dl	1055.7 (475.4)	ND	870–1,700
IgA, mg/dl	310.0 (160.0)	ND	110–410
IgM, mg/dl	124.0 (105.0)	ND	35–220
C3, mg/dl	68.2 (19.0)	ND	65–135
C4, mg/dl	28.2 (11.7)	ND	13–35
CH50, U/ml	39.5 (10.8)	ND	28–53
CTR,%	58.1 (13.0)	ND	<50

SD standard deviation; *BUN* blood urea nitrogen; *Cr* serum creatinine; *UA* uric acid; *Ccr* creatinine clearance; *CRP* C-reactive protein; *ESR* erythrocyte sedimentation rate; *RF* rheumatoid factor; *CTR* cardiothoratic ratio

peritoneal dialysis (CAPD). Usually, CAPD is not chosen in Japan to treat patients with RA because of hands or fingers impediment [15]. Little is known of the effect of HD or CAPD, or how to initiate in patients with amyloidosis associated with RA. Especially, it is difficult to determine the timing of HD initiation. If the initiation of HD is late, these patients are easy to succumb to congestive heart failure from which it's challenging to recover. We considered that to circumvent this problem, at the time of initiation, program of HD initiation is necessary.

Previously, the Cox proportional Hazard model revealed that male gender, initiation age of HD, initiation state of HD (planned or unplanned) and low levels of serum protein were significantly associated with poor survival [12]. In another previous report on HD, it was noted that male gender and low serum albumin levels are risk factors that

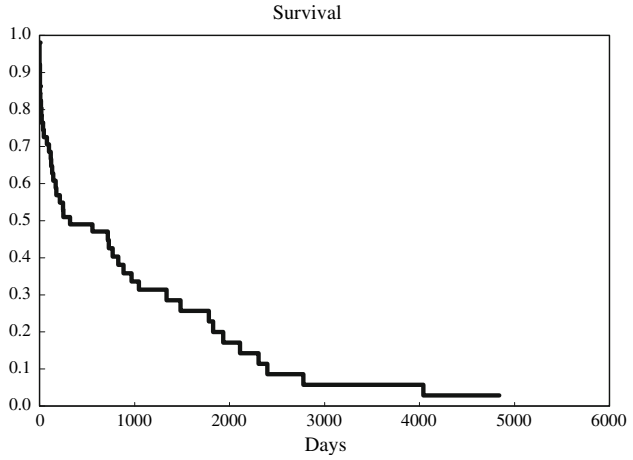

Fig. 2 Survival of hemodialysis patients. Survival in patients with hemodialysis (HD) from the initiation of HD. The Kaplan–Meier survival curve of amyloidosis patients from the initiation of HD is shown

Table 2 Cause of death in patients with amyloidosis with hemodialysis

Cause of death	*n* (%)
Heart disease	
Heart failure	23 (48.7)
Myocardial infarction	1 (2.0)
Respiratory failure	3 (6.3)
Gastrointestinal bleeding or perforation	4 (8.3)
Infections	
Shunt infection	2 (4.2)
Periodontitis	1 (2.0)
Foot ganglene	1 (2.0)
Peritonitis	2 (4.2)
Other	1 (2.0)
Malignancy	1 (2.0)
Others	
Hyperkalemia	1 (2.0)
Malnutrition	1 (2.0)
ASO	1 (2.0)
Pancreatitis	1 (2.0)
Brain hemorrhage	1 (2.0)
Unknown	4 (8.3)
Total	48 (100)

ASO Arteriosclerosis obliterans

increased the death of patients without RA [16, 17]. Our RA patients with amyloidosis showed a similar tendency as those patients who received HD. The recent Japanese survey of HD revealed that there was a significantly lower risk of death in a group of patients whom vascular access was created at 3–6 months before initiation of dialysis than in those where such access was created at the time of initiation or within 3 months before the initiation of HD [15]. These data indicated that planned initiation HD was important for the survival in patients on HD. This is in agreement with our data, whereby planned initiation of HD was critical for the survival of patients with amyloidosis associated with RA.

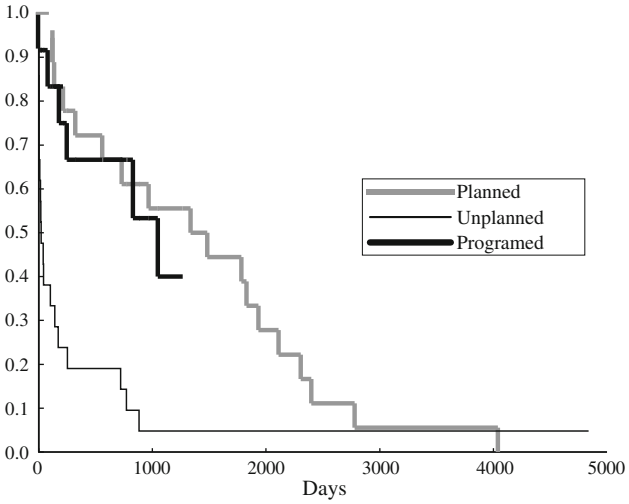

Fig. 3 Survival of planned/unplanned/programmed HD patients. Survival in patients with planned, unplanned and programmed initiation of HD. Twelve patients were treated with programmed initiation, and the others were treated with planned (20 patients) and unplanned (31 patients) initiation of HD. Patients with unplanned initiation of HD showed a significant poor survival compared with that of both planned ($P = 0.001$) and programmed initiation ($P = 0.003$). Additionally, patients with planned and programmed initiation of HD showed no significant difference in patient survival

In contrast, it is well known that serum creatinine levels of senile patients were lower than in young patients with ESRD. The serum creatinine level depends on the muscle volume. However, in patients with amyloidosis, gender, long-lasting inflammation and RA, together with low level of serum protein, were associated with a decrease in muscle volume. This may in part explain why serum creatinine levels were not elevated when compared to the Ccr levels in patients with amyloidosis associated with RA [18]. We previously demonstrated that patients with unplanned initiation of HD started therapy at the state of 2.5 mg/dl of level of Cr, whereas the equivalent Ccr was about 10 ml/min [12]. Measurement of serum creatinine was convenient to do in the outpatient setting; however, this made actual renal function difficult to estimate. Measurement of Ccr levels was considered to be useful to accurately estimate renal function even in these states. However, in patients with RA, numerous medical complications may arise due to disability. It is difficult to assess when HD was initiated. Taking these conditions into account, we planned to initiate HD safety in patients with

ESRD associated with reactive amyloidosis. The outcome of our programmed initiation was satisfactory. The survival of our twelve patients with programmed HD was significantly improved compared with that of unplanned HD patients, and the survival of programmed HD patients was not significant when compared to that of the patients with planned HD. Additionally, physical conditions of programmed HD patients were stable, and problems in relation to HD were rare. Recently, several biologics have been used for the treatment of RA. These studies showed an improvement in renal function in patients with amyloidosis associated with RA [19]. We also revealed the effectiveness of anti-TNF-α therapy, which can induce rapid resolution and sustained decrease in gastroduodenal mucosal amyloid deposits in patients with RA [20].

The use of these biologics may reduce the number of patients with amyloidosis or help in the recovery from ESRD. However, some RA patients are unable to use these drugs because of conditions such as chronic hepatitis B, HIV and tuberculosis.

In conclusion, our study demonstrates that patients with amyloidosis have a higher mortality rate. Long-term complications of HD included amyloidosis due to β2-microglobulin, neuropathy and various forms of heart disease that were difficult to avoid. In particular, increasing the frequency and length of treatments was shown to overload and cause enlargement of the heart, which is commonly seen in such patients. Nevertheless, programmed initiation of HD will improve the prognosis of patients with ESRD according to the stress of initiation. Such possibility needs to be considered in more detail in the future.

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