

## A TRIAL OF THREE REGIMENS FOR PRIMARY AMYLOIDOSIS: COLCHICINE ALONE, MELPHALAN AND PREDNISONE, AND MELPHALAN, PREDNISONE, AND COLCHICINE

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### ABSTRACT

**Background** Primary systemic amyloidosis is an uncommon disease characterized by the accumulation in vital organs of a fibrillar protein consisting of monoclonal light chains.

**Methods** We treated 220 patients with biopsy-proved amyloidosis. The patients were randomly assigned to receive colchicine (72 patients), melphalan and prednisone (77), or melphalan, prednisone, and colchicine (71). They were stratified according to their chief clinical manifestations: renal disease (105 patients), cardiac involvement (46), peripheral neuropathy (19), or other (50).

**Results** The median duration of survival after randomization was 8.5 months in the colchicine group, 18 months in the group assigned to melphalan and prednisone, and 17 months in the group assigned to melphalan, prednisone, and colchicine ( $P < 0.001$ ). Among patients who had a reduction in serum or urine monoclonal protein at 12 months, the overall length of survival was 50 months, whereas among those without a reduction at 12 months, the overall length of survival was 36 months ( $P = 0.03$ ). Thirty-four patients (15 percent) survived for five years or longer.

**Conclusions** Therapy with melphalan and prednisone results in objective responses and prolonged survival as compared with colchicine in patients with primary amyloidosis. (N Engl J Med 1997;336:1202-7.)

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**P** RIMARY systemic amyloidosis is an uncommon disease characterized by deposits of fibrillar aggregates of monoclonal immunoglobulin light chains in vital organs. These amyloid deposits cause cardiac or renal dysfunction and, ultimately, death. The Mayo Clinic reported a median duration of survival of 15 months for 132 patients in 1975 and of 12 months for 229 patients in 1983.<sup>1,2</sup> In a recent series of 474 patients seen at the Mayo Clinic within 1 month of diagnosis, the median duration of survival was 13 months.<sup>3</sup>

Because amyloid fibrils consist of monoclonal immunoglobulin light chains, treatment with alkylating agents that are effective against plasma-cell neoplasms is warranted. The results of a randomized, placebo-controlled, double-blind study of 55

patients with primary systemic amyloidosis suggested that treatment with melphalan and prednisone, which are active against multiple myeloma, was of some benefit.<sup>4</sup>

Colchicine, another drug used to treat primary amyloidosis, inhibits the induction of amyloidosis in mice and reduces abdominal pain and prevents secondary amyloidosis in patients with familial Mediterranean fever. In one report, 53 patients with primary amyloidosis seen from 1976 to 1983 who were treated with colchicine survived for an average of 17 months, whereas 29 patients seen from 1961 to 1973 who were untreated survived for an average of 6 months.<sup>5</sup> In a prospective crossover study comparing melphalan and prednisone with colchicine, those who received melphalan and prednisone had significantly prolonged survival.<sup>6</sup>

In this prospective study, patients with primary systemic amyloidosis were stratified according to their dominant clinical manifestation and then randomly assigned to receive one of the following: colchicine; melphalan and prednisone; or a combination of the three drugs.

### METHODS

#### Patients

Amyloidosis was confirmed by biopsy in every patient. Patients with secondary, familial, senile, or localized amyloidosis were not admitted to the study. Patients with overt symptomatic multiple myeloma or diarrhea were ineligible, as were patients who had previously received alkylating drugs or colchicine. The study was approved by the Mayo Institutional Review Board. All the patients gave written informed consent for participation and randomization.

#### Randomization

Patients were stratified according to the following major clinical manifestations: renal disease, including nephrotic syndrome or renal insufficiency; cardiac involvement; peripheral neuropathy; and other manifestations. Patients with more than one of these features were assigned to a group according to the most prominent characteristic. Patients were also stratified according to age and sex.

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### Medications

We used a dynamic randomization scheme (involving age, sex, and chief clinical manifestation) that ensured there would be four balanced clinical groups. The patients were assigned to treatment with colchicine (0.6 mg twice daily); melphalan (0.15 mg per kilogram of body weight) and prednisone (0.8 mg per kilogram) daily for seven days once every six weeks; or melphalan (0.15 mg per kilogram) and prednisone (0.8 mg per kilogram) daily for seven days once every six weeks plus colchicine (0.6 mg twice daily). Leukocyte and platelet counts were performed every three weeks. The daily colchicine dose was increased by 0.6 mg each week until abdominal cramps or diarrhea developed. Treatment with colchicine was then briefly discontinued and resumed at the highest dose that did not cause gastrointestinal side effects. The daily dose of melphalan was increased by 2 mg in each six-week course until mid-cycle leukopenia or thrombocytopenia developed. Patients continued to receive melphalan and prednisone for two years unless signs of serious toxicity developed. The use of colchicine was continued indefinitely.

### Measurements of Response

Responses to the three treatment regimens were assessed on the basis of the following factors: the duration of survival; improvement in renal function, as evidenced by a 50 percent decrease in the 24-hour urinary protein excretion, in the absence of progressive renal insufficiency, in patients presenting with the nephrotic syndrome (urinary protein,  $\geq 3$  g per 24 hours); a reduction in the size of the liver by at least 2 cm and a 50 percent decrease in serum alkaline phosphatase; disappearance of serum monoclonal protein or a reduction of more than 50 percent; disappearance of urinary monoclonal protein or a decrease of more than 50 percent; an increase of at least 1 g in serum albumin, given an initial value of less than 3 g per deciliter and stable renal function; and improvement in the echocardiogram with reduction in the features of amyloid infiltration, such as a decrease of 2 mm in the thickness of the interventricular septum or an increase of 20 percentage points in the ejection fraction.

### Statistical Analysis

We compared base-line values in the three treatment groups using analysis of variance, and survival curves using the log-rank test. We assessed the effect of a response to therapy on subsequent survival by using the response status at one year, among the patients alive at one year, as the grouping variable, and survival after one year as the response (the "landmark" method). All P values are two-sided. Analysis was performed with the SAS and S-Plus software packages.

## RESULTS

Of the 234 patients who were enrolled in the study between September 4, 1982, and November 20, 1992, 14 were removed from the study because we were unable to substantiate the presence of primary amyloidosis. In all 220 remaining patients there was a monoclonal immunoglobulin protein in the serum or urine or a monoclonal staining pattern of bone marrow plasma cells or amyloid fibrils with kappa or lambda antiserum. Table 1 shows the distribution of chief clinical manifestations among the three treatment groups. Of the 105 patients with renal involvement, 94 had the nephrotic syndrome. The other 11 patients with renal disease all had increased serum creatinine concentrations; in 8 patients the concentration was at least 2.0 mg per deciliter (177  $\mu$ mol per liter). In 4 of these 11 patients,

**TABLE 1.** STRATIFICATION AND RANDOMIZATION OF 220 PATIENTS WITH PRIMARY SYSTEMIC AMYLOIDOSIS.

CHIEF CLINICAL MANIFESTATION	THERAPY*			TOTAL
	C	MP	MPC	
	number of patients			
Renal disease	35	37	33	105
Cardiac involvement	16	16	14	46
Peripheral neuropathy	5	8	6	19
Other	16	16	18	50
Total	72	77	71	220

\*C denotes colchicine, MP melphalan and prednisone, and MPC melphalan, prednisone, and colchicine.

the nephrotic syndrome developed during the course of the disease. Of the 46 patients in the cardiac category, 40 had overt congestive heart failure and 37 had a ventricular septal thickness of at least 15 mm or an ejection fraction of 50 percent or less. Six patients had abnormal echocardiograms as the chief manifestation of their disease. Peripheral neuropathy was the dominant clinical problem in 19 patients. In the 50 patients with other manifestations, the chief features were liver involvement, macroglossia, weight loss, gastrointestinal symptoms, and orthostatic hypotension. Monoclonal gammopathy of undetermined importance was recognized in 41 patients (19 percent) before the diagnosis of amyloidosis.

During follow-up, the nephrotic syndrome (urinary protein excretion,  $>3.0$  g per 24 hours) developed in 14 patients. Congestive heart failure occurred in 21 patients, and peripheral neuropathy developed in only 1 patient during the course of the disease.

The three groups were similar with regard to history, results of the initial physical examination, and pertinent laboratory data at base line (Table 2). Weight loss was noted in 54 percent of the patients at randomization; the median weight loss was 9 kg (20 lb) (range, 2 to 45 kg [5 to 100 lb]). The spleen was palpable in 4 percent of the patients. Macroglossia was present in 13 percent.

A monoclonal protein was found in the serum of 71 percent of the patients — as a light chain (23 percent) or an IgG (34 percent), IgA (9 percent), IgM (4 percent), or IgD (1 percent) monoclonal protein. A monoclonal protein was detected in the urine of 70 percent of the patients. Lambda light chains predominated over kappa light chains (54 percent vs. 16 percent). The size of the urinary monoclonal protein spike was small (median, 0.41 g

**TABLE 2.** INITIAL FINDINGS IN 220 PATIENTS WITH PRIMARY SYSTEMIC AMYLOIDOSIS.

CHARACTERISTIC	THERAPY*			P VALUE
	C	MP	MPC	
	median value			
Age (yr)	64	65	63	0.98
Fatigue (% of patients)	75	71	75	0.87
Macroglossia (% of patients)	8	14	16	0.36
Palpable liver $\geq 5$ cm (% of patients)	18	13	19	0.60
Hemoglobin (g/dl)	13.5	13.7	13.2	0.63
Platelets ( $\times 10^{-3}/\text{mm}^3$ )	320	317	316	0.30
Alkaline phosphatase (IU/liter)	159	168	169	0.56
Serum creatinine (mg/dl)†	1.2	1.1	1.1	0.74
Serum monoclonal protein spike (g/dl)	0.80	0.80	1.0	0.35
Serum albumin (g/dl)	2.6	2.8	2.9	0.55
Urinary protein (g/24 hr)	2.6	2.2	2.5	0.80
Urinary monoclonal protein spike (g/24 hr)	0.36	0.40	0.51	0.93
Bone marrow plasma cells (% of nucleated marrow cells)	5	5	7	0.08
Ventricular septal thickness (mm)	14	13	14	0.45
Time from diagnosis to randomization (days)	27	20	24	0.80

\*C denotes colchicine, MP melphalan and prednisone, and MPC melphalan, prednisone, and colchicine.

†To convert values to micromoles per liter, multiply by 88.4.

**TABLE 3.** RESPONSES TO THERAPY AMONG PATIENTS WITH PRIMARY SYSTEMIC AMYLOIDOSIS.

FACTOR	THERAPY*				P VALUE†
	C	MP	MPC	REGIMENS INVOLVING MELPHALAN	
	no. with responses/ no. with abnormal values at randomization				
Serum albumin	1/50	7/42	6/42	13/84	0.03
Serum M protein	0/53	10/55	11/49	21/104	<0.001
Urinary M protein	1/55	11/51	8/48	19/99	0.002
Urinary total protein	2/35	7/36	5/32	12/68	0.23
Total no. of patients with responses	2/72	22/77	20/71	42/148	<0.001

\*A response was defined as one or more of the following: an increase of 1 g or more in the serum albumin value, given an initial value of less than 3 g per deciliter and stable renal function; disappearance of or a reduction of at least 50 percent in the serum monoclonal protein (M protein) concentration, given an initial value of at least 1 g per deciliter; disappearance of or a reduction of at least 50 percent in the urinary monoclonal protein concentration, given an initial value of at least 0.5 g per 24 hours; and a reduction of at least 50 percent in the urinary protein concentration, given an initial value of at least 3 g per 24 hours in the absence of progressive renal failure. C denotes colchicine, MP melphalan and prednisone, and MPC melphalan, prednisone, and colchicine.

†P values were calculated according to Fisher's exact test.

per 24 hours). In patients with proteinuria, the total urinary protein ranged from 0.1 to 22.4 g per 24 hours (median, 2.4); in almost one half it was  $\geq 3$  g per 24 hours. Of the 220 patients, 198 had a monoclonal protein in the serum or urine.

The results of base-line echocardiography (M-mode and two-dimensional) were abnormal in 76 percent of 219 patients. Septal thickness was at least 15 mm in 41 percent of the patients, and the ejection fraction was 50 percent or less in 26 percent of the patients. The deceleration time was 150 milliseconds or less in 23 percent (normal,  $>150$ ).

A histologic diagnosis of amyloidosis was made in all patients. Biopsy of the subcutaneous fat or bone marrow was positive in 89 percent of the patients at diagnosis. The median number of chemotherapy courses was 7 (range, 0 to 48). The melphalan dose was less than 500 mg in 51 percent and more than 2000 mg in 6 percent.

#### Response to Therapy

Table 3 shows the responses to therapy, as judged by measurements of the abnormal proteins. Forty-four patients had reductions of at least 50 percent, disappearance of serum or urine monoclonal protein, or a reduction of at least 50 percent in nephrotic-range proteinuria during the course of their disease. More than one fourth (28 percent) of the patients receiving melphalan and prednisone, but only 3 percent of the colchicine-treated patients, had a decrease in these factors (Table 3). Of the patients who responded to therapy as judged by the criteria listed in the Methods section as well as by measurements of the abnormal proteins, 70 percent did so within one year after beginning chemotherapy. Twenty-one percent of the patients required an additional year of therapy to show a response. Of the 44 patients who responded to therapy, 32 responded in one of the categories, 7 responded in two of the categories, 4 responded in three of the categories, and 1 responded in four of the categories.

Six of 12 patients treated with melphalan who had serum alkaline phosphatase values of more than 500 IU per liter and palpable livers had reductions of at least 50 percent in the serum alkaline phosphatase value (median, 592 IU per liter; range, 414 to 2367) and a decrease in liver size (median, 4 cm; range, 2 to 8). None of the colchicine-treated patients with hepatic amyloidosis responded to treatment.

Two patients had objective reductions in septal thickness, increased ejection fractions, and overall improvement on their echocardiograms.

Renal failure necessitating dialysis developed in 41 patients — 15 in the colchicine group, 16 in the group assigned to melphalan and prednisone, and 10 in the group assigned to melphalan, prednisone, and colchicine ( $P=0.64$ ). There was no significant difference between treatment groups in the time from ran-

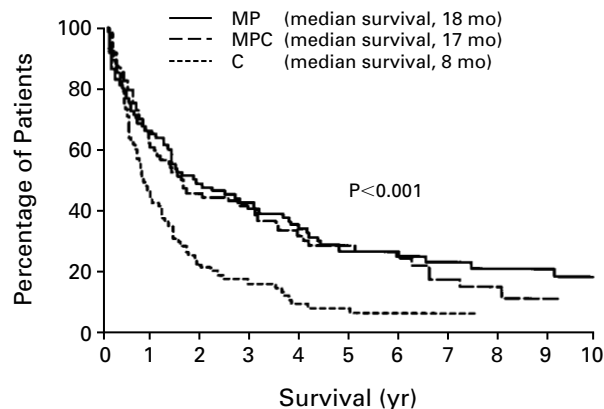
domization to the time when dialysis was needed. One additional patient had begun dialysis three weeks before randomization. The median duration of survival from the beginning of dialysis, for all treatment groups, was 14 months with peritoneal dialysis and 9 months with hemodialysis.

Myelodysplasia developed in 7 of the 148 patients receiving melphalan, and acute leukemia in 1. The time from the beginning of chemotherapy to the diagnosis of myelodysplasia or acute leukemia ranged from 26 to 69 months (median, 35), and the dose of melphalan ranged from 421 to 1792 mg (median, 1235). There were abnormalities of chromosomes 5 or 7 in four of the six patients who had cytogenetic studies. Four of the eight patients in whom myelodysplasia or leukemia developed died of the disease. One other patient was found to have monosomy 7 on two bone marrow examinations but was alive and without cytopenia 10 years later.

Two patients had rupture of the spleen, and one had rupture of the liver. Two patients received heart transplants, and one received a kidney transplant. All three were doing well two, three, and seven years after transplantation, respectively.

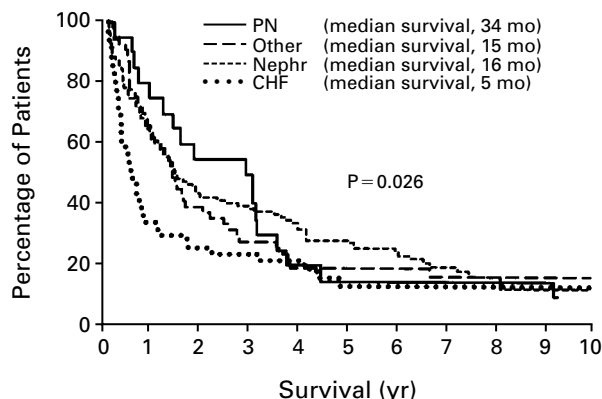
#### Survival

The median duration of survival from randomization was 8 months for the colchicine group, 18 months for the group assigned to melphalan and prednisone, and 17 months for the group assigned to melphalan, prednisone, and colchicine ( $P<0.001$ ) (Fig. 1). Patients with cardiac amyloidosis had a much shorter survival after randomization (5 months) than those with peripheral neuropathy (34 months) (Fig. 2). In the patients with cardiac involvement, those treated with melphalan survived significantly longer



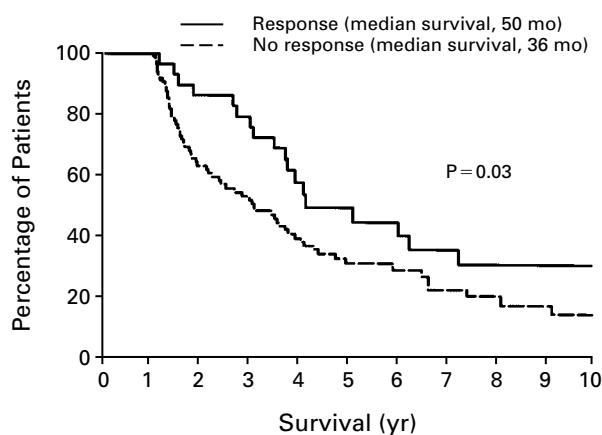
**Figure 1.** Survival from the Date of Randomization among Patients with Primary Systemic Amyloidosis, According to Treatment Group.

MP denotes melphalan and prednisone, MPC melphalan, prednisone, and colchicine, and C colchicine.



**Figure 2.** Survival from the Date of Randomization among Patients with Primary Systemic Amyloidosis, According to the Chief Clinical Manifestation.

PN denotes peripheral neuropathy, Nephro the nephrotic syndrome or renal insufficiency, and CHF congestive heart failure.



**Figure 3.** Survival from the Date of Randomization among Patients with Primary Systemic Amyloidosis, According to Whether They Had Had Serum or Urinary Protein Responses by the End of 12 Months.

than those treated with colchicine. An analysis at 12 months revealed that patients with serum or urinary protein responses had a median overall survival of 50 months, whereas the median overall survival was 36 months for those without an objective response ( $P=0.03$ ) (Fig. 3). The labeling index (percentage of plasma cells in the S phase) for bone marrow plasma cells did not predict survival (data not shown).

Cardiac causes accounted for most of the deaths (51 percent). It is likely that several of the patients whose cause of death was given as amyloidosis (18 percent) actually died of a cardiac cause. Renal insufficiency and infection accounted for 15 percent of the deaths.

### Long-Term Survival

Thirty-four patients (15 percent) survived for five years or longer after diagnosis of primary systemic amyloidosis. Renal involvement was the chief clinical manifestation in 20 of these patients; only 3 of the 34 had cardiac amyloidosis. Of the 34 patients, 3 had been randomly assigned to receive colchicine, 17 to receive melphalan and prednisone, and 14 to receive melphalan, prednisone, and colchicine. No changes in serum or urinary proteins or reduction in liver size and serum alkaline phosphatase values occurred in the three patients receiving colchicine. No measurement we made differentiated the long-term survivors from the remainder, but patients who had objective responses were more likely to survive for five years (17 of 34) than those who did not (13 of 90) ( $P<0.001$ ). Five patients lived for more than 10 years.

### DISCUSSION

Current therapy for primary systemic amyloidosis is unsatisfactory. In a double-blind study<sup>4</sup> of 55 patients with primary amyloidosis, those given melphalan and prednisone therapy benefited. That trial was followed by a randomized, crossover study of melphalan and prednisone compared with colchicine.<sup>6</sup> Of 101 patients who were stratified according to their dominant clinical manifestations, 49 were randomly assigned to receive melphalan and prednisone, and 8 subsequently crossed over to colchicine; 35 of 52 patients who were randomly assigned to receive colchicine crossed over to melphalan and prednisone because their disease had progressed. There was no significant difference in duration of survival between the two groups (melphalan and prednisone, 25 months; colchicine, 18 months). However, significant differences favoring melphalan and prednisone were found when the survival of patients who received only one of the treatments was analyzed or when survival was determined from the time of entry into the study to the time of death or progression of disease ( $P=0.001$ ).<sup>6</sup> This finding led to the current study. A recent report on 100 patients with primary systemic amyloidosis randomly assigned to receive either colchicine or the combination of melphalan, prednisone, and colchicine reported longer survival with the regimen containing melphalan (12 vs. 7 months).<sup>7</sup>

The results of therapy in primary amyloidosis are difficult to document, because the total amount of amyloid in a patient is impossible to measure accurately. Imaging with <sup>125</sup>I-labeled human serum amyloid P component is useful for locating and monitoring the extent of systemic amyloidosis, because the P component is present in all types of amyloid.<sup>8</sup> Small deposits of amyloid, such as those in carpal ligaments, can be visualized, but uptake by the heart and kidney may be obscured by the high blood flow in these organs. In addition, the procedure is expensive. Currently, investigators are limited to determin-

ing survival, evaluating organ function, and measuring the monoclonal protein in the serum and urine.

The symptoms, physical findings, and laboratory-test results of the patients in this study were not different from those found in a large, unselected cohort of patients with primary systemic amyloidosis.<sup>3</sup> The median duration of survival was longer in the two groups assigned to regimens involving melphalan (17 and 18 months) than in the group receiving colchicine (8 months). Survival was shorter (5 months) in those with major cardiac involvement than in those with the nephrotic syndrome (16 months), other manifestations (15 months), or peripheral neuropathy (34 months). There was no difference among the three treatment groups in the incidence or duration of therapy until dialysis was required for renal insufficiency.

Although therapy with melphalan and prednisone resulted in objective responses and prolonged survival as compared with colchicine, treatment is still inadequate. More intensive therapy consisting of high-dose chemotherapy followed by rescue with peripheral stem cells shows promise.<sup>9</sup> High-dose dexamethasone has been reported to be beneficial in primary systemic amyloidosis.<sup>10</sup> The introduction of 4'-iodo-4'-deoxydoxorubicin, which has an affinity for amyloid fibrils, may represent the addition of an important treatment option for primary systemic amyloidosis.<sup>11</sup>

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