Primary systemic amyloidosis (AL) is a rare disorder characterized by production of an aberrant monoclonal light chain. This insoluble light chain, or a fragment thereof, deposits in tissues as amyloid and results in disruption of organ function and, ultimately, death. Although melphalan and prednisone were reported to benefit subsets of patients with the disease, many patients showed no benefit; the median survival with the disease is ~2 years. There is a need to develop new agents for patients who fail to respond to a trial of cytotoxic chemotherapy. A study was undertaken of interferon alfa-2 in the treatment of 15 patients with AL because of its reported benefits in the induction and maintenance therapy for patients with multiple myeloma, a disease that has many characteristics in common with AL. None of the patients showed any objective regression of their disease; the median survival of the entire group was 26.3 months. This survival is not superior to that reported with other agents used for this disease. We conclude that interferon alpha-2 is not a valuable agent in the treatment of AL.

Key words: cardiomyopathy, nephrotic syndrome, AL

INTRODUCTION

Primary systemic amyloidosis (AL) is a plasma cell dyscrasia. Patients with AL produce a monoclonal light chain or a fragment thereof that can deposit as amyloid in organs and disrupt their function [1,2]. Purification of the light chain from the urine of humans with AL and its injection into mice reproduce the disease [3]. Although AL is a clonal disease, it is not a malignancy.

In spite of the fact that AL is not a malignant disorder, melphalan and prednisone have been used successfully in its treatment [4-12]. The presumed mechanism is the cytotoxic effect this combination has on the bone marrow plasma cells, which are the source of the amyloidogenic light chains [13]. Many patients show no demonstrable benefit from melphalan and prednisone, and the median survival of patients with this disease is ~2 years [14].

Recombinant interferon alpha-2b showed promising effects in multiple myeloma [15,16]. Interferon was reported to increase the response rate and number of complete responses in patients with multiple myeloma [17]. It was also demonstrated to be beneficial in maintenance of patients with myeloma [18,19]. Interferon may also be synergistic with chemotherapy in the treatment of multiple myeloma [20]. The benefits of interferon and the most durable responses were reported in patients whose tumor burden was low [21-23]. Among six responsive myeloma patients in one study, two had stage I and three had stage II disease [24]. Based on this information, it was logical to consider interferon alfa-2 in patients with biopsy-proven AL who had failed traditional cytotoxic chemotherapy.

MATERIALS AND METHODS

Fifteen patients with biopsy-proven AL were entered into the study. Accrual of patients occurred from May, 1988, through October, 1991. Patients with secondary, familial, or localized amyloidosis were excluded. No patient had multiple myeloma associated with AL. All 15 patients had been treated previously with melphalan and prednisone; nine also had received colchicine therapy. One patient had been treated with cyclophosphamide, and one patient had been treated with vitamin E. Patients were treated continuously with interferon alpha-2b (kindly supplied by Schering Corp., Kenilworth, NJ) at...
an initial dose of $2 \times 10^6$ U/M$^2$, three times per week. If the dose was well tolerated without excessive interferon side effects, such as nausea, fatigue, anorexia, and flu-like symptoms, the dose was increased 50% per month. Patients were treated until death or until progression of their disease. No patient received concomitant therapy with melphalan, prednisone, or colchicine. No patient had prior exposure to interferon-alpha. No initial modification of the interferon dose was made for those patients with renal insufficiency at presentation. The study design used the standard single-stage test procedure, which allowed for early termination of the study while preserving size and power of the single-stage procedures modified by Fleming [25]. The study was approved by the Institutional Review Board of the Mayo Foundation, and all patients gave written informed consent prior to entry into the study.

RESULTS

The characteristics of the patients are given in Table I. Eight of the 15 patients died. Seven patients are alive with a minimum follow-up of 27 months. Each patient was classified according to the dominant organ of involvement. Of two patients classified under “other,” one presented with amyloid lymphadenopathy and amyloid-related pleural effusion with cardiomyopathy, and the other patient presented with alveolar septal pulmonary amyloid [26].

The diagnosis of AL could generally be established by less invasive diagnostic tests such as subcutaneous fat (seven of nine), marrow (10 of 13), and rectal biopsy (four of five). We resorted to visceral organ biopsy when the results of less invasive studies were inconclusive. The production of M protein in our patients was modest—median serum level 0.75 g/dl (range 0.3–2 g/dl). Serum immunoelectrophoresis revealed a monoclonal Aλ in three patients, Gk in three, Gκ in one, Dλ in one, and free λ chains in two. Only three of the 11 patients with a urinary M protein had a urine M spike $>1$ g/24 hr. Two patients had κ and nine had λ immunoglobulins.

Patients were treated with interferon at a dose range of $1.8 \times 10^6$ units to $8 \times 10^6$ units. The median interferon dose for all 15 patients was $3.8 \times 10^6$ units. All patients were treated for a minimum of 1 month. The median duration of treatment was 6.5 months, and one patient remains on treatment with interferon at 27 months.

All eight deaths in our study occurred because of progressive AL. Three patients died of refractory cardiac failure, and three died of cardiac arrest presumed to be due to ventricular arrhythmias related to cardiac amyloid. One patient with diffuse alveolar septal pulmonary amyloid died of respiratory failure, and one patient died of pneumonia, presumably related to bed confinement, which was a result of advanced peripheral and autonomic amyloid neuropathy.

The actual median survival of the entire group is 26.3 months. This is not different from other reported survivals in treated patients with AL and represents no comparative improvement [27]. The three longest survivors are at 41, 46, and 48 months. The first two are receiving dialysis, and the last one had sensory peripheral neuropathy without autonomic features.

DISCUSSION

Interferon alpha-2 has been shown to have multiple effects on cellular and humoral immunity and is classified...
as an immune modulator [28,29]. The mechanism by which interferon produces its clinical benefit in myeloma, whether inhibition of cellular proliferation or direct tumor cytotoxicity, is not yet known.

In this study, interferon alfa-2 produced no objective benefit in the treatment of AL. In spite of the encouraging results reported for multiple myeloma, no disease regression was seen, and the median survival of this group did not differ from that in other large series of AL patients treated in alternative fashions. Duston et al. [30] reviewed their experience with 146 amyloid patients and found a median survival of 22.4 months. Kyle and colleagues [11,12] showed that treatment with melphalan and prednisone in two different study populations resulted in median survivals of 11 and 25.2 months. Treatment with colchicine resulted in a median survival of 18 months [31]. The median survival of 401 patients seen at the Mayo Clinic from 1982 to 1987 was 2 years [32]. Median survival for patients with peripheral neuropathy, however, is >5 years. In most published studies, cardiac deaths account for approximately one-half the deaths. Because of the more widespread application of dialysis for patients who go on to end-stage renal disease, renal failure as a cause of death is infrequent. The three dialysis patients in this study who died did so as a result of cardiac failure.

All nonrandomized studies of AL must be interpreted with caution, because the mix of patients with the various amyloid syndromes can have a significant impact on survival. There is also a risk that patients seen recently will have the diagnosis of AL made earlier in the disease course because of the more widespread recognition of this disorder by clinicians and the widespread introduction of less invasive diagnostic tests, such as the subcutaneous fat aspirate test, that result in an earlier diagnosis [32]. We conclude, in spite of the beneficial effect interferon shows on the plasma proliferative disorder multiple myeloma, that in AL its use is unjustified and should be avoided.

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REFERENCES


