Treatment of AL Amyloidosis with 4′-Iodo-4′-Deoxydoxorubicin: An Update

To the Editor:

Amyloidosis formed by monoclonal immunoglobulin light chain (AL) is a rapidly progressive disease in most patients, causing organ failure and death within 1 to 3 years of diagnosis.[1,2] The logical therapeutic target in this type of amyloidosis is the elimination of the offending light chain by the annihilation of the clone producing it. This approach has recently been substantiated by reports documenting important clinical benefit with occasional complete clinical recovery following suppression of light-chain–synthesizing clones obtained by high-dose chemotherapy followed by autologous stem-cell transplantation.[3] The observation that a new anthracycline, 4′-iodo-4′-deoxydoxorubicin (I-DOX), can reduce the amyloid load without affecting the level of circulating light chain has shown for the first time the possibility and feasibility of interacting directly with the amyloid deposits.[4] Here we report the results observed in 14 more patients treated with I-DOX at our Institutions (institutional cases) and outline the results available from the European compassionate program (compassionate cases).

Between February 1, 1995 and December 1, 1997, 14 patients were enrolled and gave written informed consent as approved by our Institutional Review Board. Amyloidosis was confirmed by biopsy in every patient, and the monoclonal light chain was detected by serum or urine immunofixation. The patient characteristics at enrollment are reported in Table 1. Nine of the 14 institutional patients had been previously treated with alkylating agents without benefit. In the same period, 28 AL patients were treated with I-DOX on a compassionate basis in several European countries. The data available for these patients are incomplete, as reported in Table 1, and aspects relevant to treatment outcome, such as performance status, were occasionally missing or could not be verified.

Thirteen of the institutional patients were treated with courses of I-DOX consisting of 10 to 30 mg/m^2 weekly dose for 4 consecutive weeks; 6 patients were treated with a single course, 6 with 2, and 1 with 3 courses, at a median interval of 7 months (range 3 to 16). In 1 patient, rapidly progressing disease permitted administration of a single I-DOX dose. This patient was not evaluable for response. The criterion for administering an additional I-DOX cycle in responsive patients or in patients who achieved stabilization of the disease was the occurrence of signs of progression. In 3 patients I-DOX was followed by treatment with melphalan and prednisone (MP), and in 2 others by high-dose melphalan followed by stem-cell rescue (HDCT). In these 5 patients the response to I-DOX was evaluated before starting the alkylating-agent–based chemotherapy. The 28 compassionate patients were treated with I-DOX at 15 to 30 mg/m^2 weekly dose for 4 consecutive weeks: 17, 7, 1, and 3 patients were treated with 1, 2, 3, or 4 courses, respectively. Response was defined by evidence of reduced amyloid load as assessed with echography, computed tomography, magnetic resonance imaging, or scintigraphy with serum amyloid P component (SAP)[5] or aprotinin,[6] and/or by improvement of one or more affected organ(s) as follows: (1) kidney, ≥50% reduction in 24-hour urine protein excretion in the absence of progressive renal insufficiency; (2) heart, ≥2 mm decrease in interventricular septum thickness or improvement of ejection fraction by ≥20%; (3) liver, ≥50% decrease in or normalization of alkaline phosphatase level, and/or reduction in the size of the liver ≥2 cm; (4) neuropathy, clinical improvement supported by electromyography. Only one parameter was required to satisfy the response criteria.

Six of the 13 evaluable institutional patients were responsive, and 4 showed stable disease. Onset of clinical/instrumental improvement could be delayed up to 3 months after therapy. Median duration of clinical benefit was 7 months. Best results were obtained in patients with soft tissue involvement, whereas those with heart, kidney, or liver involvement did not experience recovery of organ function. In the 7 patients treated with more than one course of I-DOX, the most marked effect was noticed after the first course, whereas the following courses generally stabilized the result without offering further improvement. Hematologic and extrahematologic toxicity was mild and uneventful; occasionally a sudden, partially reversible functional deterioration of the amyloid target organ (kidney) was observed immediately after I-DOX administration. Crude median survival from first I-DOX dose was 21.5 months (range: 2 to 37). As of September 30, 1998, 10 patients died of causes related to amyloidosis and 4 are still living. Overall, 5 patients were shifted to other treatment with MP (n = 3) or HDCT (n = 2). Three of these patients died in spite of the new treatment at 22, 24, and 26 months respectively, from first I-DOX. The contribution of I-DOX to survival could not be reliably estimated due to the small number of cases and the confounding effect of introducing new treatments. The data available from the European compassionate program are fragmentary and incomplete. Of the 28 patients for whom we had at least partial feedback, a response was observed in 5 patients, in 11 patients I-DOX stabilized the disease, 11 patients did not respond to I-DOX therapy, and the disease progressed to death in most of them. Two patients with severe heart involvement died suddenly within a few days after I-DOX therapy, and in another the effect of I-DOX was not evaluable for lack of information. Sufficient data on hematologic toxicity were not obtained. Serious adverse events were reported in 3 patients: the 2 sudden deaths reported above and 1 patient who went into acute renal failure immediately after I-DOX administration. Other side effects consisted of nausea and vomiting less than or equal to grade 2.

Overall, this update confirms our preliminary report of activity, but it also indicates that only a minor proportion of AL patients responded to I-DOX as used and that clinical effects were transient and insufficient to affect the course of the disease. These results should not be viewed as conclusive evidence against I-DOX because much remains to be learned about the mechanism, the dosing, and the optimal setting for the best use of the drug. Also, a phase II trial, coordinated by the National Cancer Institute, is now starting in the United States to clarify, among other points, these aspects. However, the hypothesized mechanism of action of the drug, ie, specific interaction with amyloid deposits with possible promotion of their resorption, makes it unlikely that I-DOX alone could significantly improve the course of the disease while continuous production and deposition of amyloidogenic monoclonal light chains persist. At present, it appears that this drug should be used as an adjunct to more specific and effective treatment for AL amyloido-

Table 1. Patient Characteristics at Enrollment

	Institutional	Compassionate
Number	14	28
Median age (range)	57 (46-73)	56 (46-68)
Men/women	10/4	17/11
M-component: lambda/ kappa/not specified	13/1/0	11/4/13
ECOG performance status: 1/2/3/not specified	7/5/2/0	2/19/4/3
Prior chemotherapy: yes/ no/not specified	9/5/0	22/2/4
Dominant organ involvement:		
Kidney/heart	4/1	9/4
Liver/peripheral nervous system	1/2	3/4
Soft tissues/other	5/1	2/6

sis, such as high-dose chemotherapy with autologous stem-cell support or conventional MP treatment.

Giampaolo Merlini
Ernesto Anesi
Pietro Garini
Vittorio Perfetti
Laura Obici
Edoardo Ascari
Biotechnology Research Laboratories
Internal Medicine & Medical Oncology
University Hospital-IRCCS Policlinico S. Matteo
Pavia, Italy
Maria J. Lechuga
Clinical Development
Pharmacia & Upjohn
Milan, Italy
Giuseppe Capri
Luca Gianni
Division of Medical Oncology
Istituto Nazionale Tumori
Milan, Italy

REFERENCES

1. Kyle RA, Gertz MA: Primary systemic amyloidosis: Clinical and laboratory features in 474 cases. Semin Hematol 32:45, 1995

2. Merlini G, Marinone MG, Anesi EF, Ascari E: Report of an Italian study protocol on AL amyloidosis. Blood 84:179a, 1994 (abstr)

3. Comenzo RL, Vosburgh E, Falk RH, Sanchorawala V, Reisinger J, Dubrey S, Dember LM, Berk JL, Akpek G, LaValley M, O'Hara C, Arkin CF, Wright DG, Skinner M: Dose-intensive melphalan with blood stem-cell support for the treatment of AL (amyloid light-chain) amyloidosis: Survival and responses in 25 patients. Blood 91:3662, 1998

4. Gianni L, Bellotti V, Gianni AM, Merlini G: New drug therapy of amyloidoses: Resorption of AL deposits with 4′-iodo-4′-deoxydoxorubicin. Blood 86:855, 1995

5. Hawkins PN, Aprile C, Capri G, Viganò L, Munzone E, Gianni L, Pepys MB, Merlini G: Scintigraphic imaging and turnover studies with iodine-131 labelled serum amyloid P component in systemic amyloidosis. Eur J Nucl Med 25:701, 1998

6. Aprile C, Marinone G, Saponaro R, Bonino C, Merlini G: Cardiac and pleuropulmonary AL amyloid imaging with technetium-99m labelled aprotinin. Eur J Nucl Med 22:1393, 1995

Liver Transplantation in a Hemophilia Patient With Acquired Immunodeficiency Syndrome

To the Editor:

Recent progress in the treatment of AIDS, specifically protease inhibitor combination antiretroviral therapy, has delayed disease progression, improved immune function, and reduced mortality.[1,2] These advances prompted us to undertake liver transplantation in a 38-year-old man with moderate hemophilia A, FVIII: C = 0.03 U/mL, HIV infection since 1985, AIDS with a CD4 160/μL, and hepatitis C (HCV) end-stage liver disease. Antiretroviral therapy with lamivudine and stavudine was begun in January 1997, when the CD4 lymphocyte count was 160/μL and HIV RNA polymerase chain reaction (PCR) was 12.0×10^3 copies/mL, and nelfinavir was added 3 months later, when the HIV RNA PCR was 4.8×10^3 copies/mL. Esophageal variceal bleeding in April 1997 and progressive jaundice and hepatic encephalopathy led to transplantation in September 1997.

Laboratory studies revealed ammonia (NH_3) 90 μmol/L (normal [nl] range, 9 to 33), platelets 89,000/μL, alanine transaminase 77 IU/L (nl < 40), aspartate transaminase 103 IU/L (nl < 40), bilirubin 4.1 mg/dL (nl, 0.3 to 1.3 mg/dL), and protime (PT) 19.9 seconds. An ultrasound confirmed ascites, splenomegaly, and a small liver, and computerized tomographic (CT) scanning confirmed cirrhosis and portal hypertension. He was anergic, with no response to PPD, mumps, or tricophyton. The anti-HBs, anti-HBc, anti-HCV, anti-HAV, and EBV VCA IgG were positive, and the HBsAg, CMV IgG, EBV ENA, EA, and VCA IgM were negative. The HCV RNA PCR was 128×10^5 Eq/mL. The CD4 lymphocyte count was 156/μL (17%) and the HIV RNA PCR less than 0.4×10^3 copies/mL.

Liver transplantation was performed by standard piggyback placement.[3] The donor was positive for CMV IgG and negative for antibodies to HIV 1 and 2, HTLV-1, and HIV antigen, HBsAg, anti-HBc, and anti-HCV. A total of 29 U of packed red cells, 34 U of fresh frozen plasma, 12 U of platelets, and 15,900 U of recombinant factor were infused during the 9-hour procedure. No factor VIII was required after 7 hours. The recipient liver showed pathologic evidence of micronodular cirrhosis and excess iron.

Postoperative medications included antirejection therapy with tacrolimus (FK506) and prednisone, antiretroviral drugs, including nelfinavir, lamivudine, and stavudine, and prophylactic trimethoprim-sulfamethoxazole and acyclovir. The clinical course was complicated by mild respiratory insufficiency from volume overload, an abdominal incisional wound infection responsive to antibiotics, and a petit mal seizure from high FK506 plasma levels, resulting from nelfinavir inhibition of cytochrome P450 3A and resolved when FK506 dosing was reduced to once weekly. Transient CMV antigenemia ($pp65^+$) responded to intravenous oral ganciclovir, with subsequent CMV IgG seroconversion (Fig 1). The HIV viral load is persistently negative, and the CD4 was 256/μL by day 210.

Although AIDS has been an absolute contraindication to transplantation,[4] the better outcome of our patient than past recipients[5] suggests transplantation may be safe in AIDS patients receiving highly active antretroviral therapy. Given the potential clinical scenarios, eg, past opportunistic infections, persistently detectable HIV viral load, antiretroviral therapy intolerance due to liver dysfunction, and an unknown durability of immunologic recovery, it is critical to begin prospective clinical trials to determine the safety and efficacy of transplantation in AIDS and end-stage liver disease.

Margaret V. Ragni
S. Forrest Dodson
Susan C. Hunt
Franklin A. Bontempo
John J. Fung
University of Pittsburgh School of Medicine
Pittsburgh, PA