Original Study

Primary Amyloidosis With Renal Involvement: Outcomes in 77 Consecutive Patients at a Single Center

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Abstract

In primary amyloidosis toxic clonal immunoglobulins damage and deposit in the heart, kidneys and other organs. We report on 77 consecutive patients with primary amyloidosis and renal involvement treated and followed over a 7-year period. Although two thirds achieved deep hematologic responses with chemotherapy, over a third progressed to ESRD, an outcome highlighting the hitherto unmet need for anti-amyloid therapy.

Background: Outcomes in primary amyloid renal patients are of interest as the era of monoclonal antibody therapies begins. **Patients and Methods:** We studied 77 consecutive primary amyloid renal patients (58% men) for renal progression (end stage renal disease [ESRD]), renal response (RR), and overall survival (OS). **Results:** At diagnosis median age was 63 (range, 35-81) years, estimated glomerular filtration rate 70 mL/min (range, 5-114), difference between involved and uninvolved free light chains 127 mg/L (range, 1-9957), ESRD 4%, renal stage 2 and 3 78%, and cardiac stage 2 and 3 56%. Ninety-six percent received bortezomib and 44% stem cell transplantation as well as bortezomib, 68% achieved complete or very good partial hematologic response (CR/VGPR), 34% had ESRD, and 39% RR. Median times to ESRD and RR were 18 (range, 3-81) and 12 (range, 2-30) months, respectively. Median OS was not reached in this cohort and was not reached from onset of ESRD. More than two-thirds of patients with ESRD also achieved CR/VGPR. In those without ESRD at diagnosis, baseline creatinine and absent RR predicted progression to ESRD in multivariate Cox regression analysis, whereas CR/VGPR predicted RR. In multivariate Cox regression analysis, cardiac stage and achievement of CR/VGPR predicted OS, enabling construction of a prognostic model. **Conclusion:** Anti-plasma cell therapies provide a definite albeit limited benefit and new approaches to amyloid-related organ dysfunction are needed.

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Introduction

In primary amyloidosis the toxicity as well as fibrillar deposition of abnormal immunoglobulin proteins produced by clonal plasma cells cause organ damage.[1] Deep hematologic responses to anti-plasma cell therapy halt significant aberrant protein production and thus are major predictors of survival.[2] However, reversal of organ damage despite an adequate hematologic response might be delayed or might not occur. Moreover, patients with advanced cardiac involvement at diagnosis have poorer survival despite hematologic responses.[3] Hence, cardiac stage on the basis of the biomarkers N-terminal pro b-type natriuretic peptide (NT-proBNP) and troponin at diagnosis predicts risk to survival in patients with primary amyloidosis,[4] and specifically measured cardiac responses using increases and decreases in NT-proBNP have been clinically validated as useful surrogates for survival in clinical research.[5] Moreover, with the availability of effective anti-plasma cell agents such as bortezomib and risk-adapted melphalan with stem cell transplantation

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(SCT), the course and survival of patients with primary amyloidosis have improved.[6-9]

The determinants of organ improvement or worsening after anti-plasma cell treatment remain incompletely understood,[5,10,11] although the kinetics of organ response after normalization of the serum free light chain ratio have been reported.[12] Many patients, however, do not achieve normalization of the ratio and, as renal progression occurs, the utility of the serum free light chain assay diminishes.[2] Furthermore, many patients experience deep hematologic responses with anti-plasma cell therapy, procuring the benefit of prolonged survival, but do not experience organ improvement; indeed, progression of organ disease often occurs despite achievement of such responses.[13] The kidneys are involved in more than 60% of newly diagnosed patients.[3,14] The utility of renal staging and the definition of renal progression and response have heightened our ability to design clinical trials and to guide patients with respect to the risk of organ failure and progression to end stage renal disease (ESRD). As therapies have improved, however, a fuller appreciation of the natural history of renal involvement might be helpful in this period when the rates of deep hematologic responses are higher than ever. With this backdrop, a real-world analysis might help us to appreciate the context in which anti-plasma cell as well as anti-amyloid monoclonal antibody therapies for primary amyloidosis are being developed.[11,15]

We report on 77 consecutive primary amyloid patients with renal involvement seen from 2008 to 2015. Almost all of them received bortezomib-based therapy, almost half underwent autologous SCT, and more than two-thirds achieved complete (CR) or very good partial hematologic response (VGPR). As is the case in patients with monoclonal gammopathies associated with renal injury (including multiple myeloma), bortezomib is a critically important agent with significant renal benefits, SCT can be safely performed even in patients receiving dialysis, and achievement of a deep hematologic response is crucial to reversing or halting paraprotein-related renal injury.[16,17] In this report we focus our analysis on the course of progression to ESRD and on renal responses (RRs), and on the variables that influence both, as well as on the construction of an algorithm for risk to overall survival for patients with primary amyloidosis with renal involvement. The results of these analyses might be particularly useful as we enter a new era of monoclonal antibody therapies, anti-amyloid as well as anti-plasma cell.

Patients and Methods

We identified consecutive biopsy-proven primary amyloidosis patients with renal involvement at diagnosis in an institutional review board-approved database of patients diagnosed between July 1, 2008 and June 30, 2015 seen and followed at our center.[18] Data collection was completed on December 1, 2016. Time from diagnosis to being seen at our center and to first treatment was recorded. Epidemiologic and clinical characteristics included age, sex, cardiac and renal stage, estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration, features of monoclonal gammopathies, serial paraprotein measurements, specific therapies, and hematologic, cardiac, and RRs assessed using established criteria.[2,14,19] Response calculations are reported according to intention to treat except as otherwise noted. Overall survival was calculated from the date of starting therapy to the date of last contact or death. We used Kaplan–Meier (log rank) analyses and Cox regression to investigate variables associated with progression to ESRD, RR, and overall survival. Cox models were fitted to compute predictors, hazard ratios, and 95% confidence intervals on the basis of a 3-month landmark analysis for renal progression to ESRD and RR, and for identification of predictors of overall survival from start of therapy, using baseline clinical data, and hematologic and organ response variables. Variables of statistical significance ($P \leq .15$) in univariate analyses were included in multivariate analyses. MedCalc version 17.5.5 (MedCalc Software, Ostend, Belgium) was used for all statistical analyses.

Results

Patients

We report on 77 consecutive patients with newly diagnosed primary amyloidosis (amyloidosis light-chain type (AL) = 75, amyloidosis heavy-chain type (AH) = 1, AH/AL = 1) with renal involvement seen from 2008 to 2015. The median age of the cohort was 63 (range, 35-81) years and 45 were men (58%); patient characteristics are shown in Table 1.[5,20] There were no differences between the 11 patients with previous monoclonal gammopathies and the other 66 with respect to age, sex, difference between involved and uninvolved free light chains (dFLC), or cardiac or

Table 1 Patient Characteristics

Characteristic	Value
Age at Diagnosis, y	63 (35-81)
Male Sex	45 (58)
Months From Diagnosis to Center	1 (0-42)
Months From Diagnosis to Therapy	1 (1-5)
Previous Carpal Tunnel Syndrome	5 (6)
Previous MGUS or Myeloma	8 (10)
Waldenström macroglobulinemia	3 (4)
Marrow Clonal Plasma Cells	10 (1-70)
Clonal λ Light Chain Isotype	68 (88)
Involved FLC, mg/L	183 (13-9970)
dFLC, mg/L	127 (1-9957)
Organs Involved, n	2 (1-5)
Renal	77 (100)
Heart	46 (60)
GI tract	16 (21)
PNS	10 (13)
Other	5 (6)
Renal Stage I/II/III, n	17/38/22
Proteinuria, g Per 24 h	6.9 (0.74-26)
Serum Creatinine, mg/dL	1.03 (0.55-15.4)
Alkaline Phosphatase, mg/dL	73 (38-483)
Cardiac Stage I/II/III	3/22/21
BNP, pg/mL[a]	145 (16-3047)
Troponin-I, ng/mL	0.03 (<0.03-9)

Data are presented as median (range) or n (%), except where otherwise noted.
Abbreviations: BNP = brain natriuretic peptide; dFLC = difference between involved and uninvolved free light chains; GI = gastrointestinal; MGUS = monoclonal gammopathy of undetermined significance; NT = N-terminal; PNS = peripheral nervous system.
[a]Conversion between BNP and NT-proBNP for staging and response is: log BNP = 0.28 + 0.66 × log NT-proBNP (Merlini et al[5] and Dimopoulos et al[20]).