blood advances

COUNTERPOINT Delay treatment of AL amyloidosis at relapse until symptomatic: devil is in the details

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This article has a companion Point by Palladini and Merlini.

Systemic immunoglobulin amyloid light-chain (AL) amyloidosis is associated with a small B-cell clone in the form of a plasma cell dyscrasia causing deposits of amyloid fibrils derived from misfolded immunoglobulin light chains in various organs and tissues. Progress with the advent of biomarkers of plasma cell clone and organ dysfunction allowing for appropriate treatment selection by risk stratification,[1] recognition of plasma cell clone biology,[2,3] and response to treatment[4-6] and availability of novel therapeutic agents have dramatically improved survival[7] and outlook for patients with AL amyloidosis over the past few decades. Furthermore, surrogate markers of hematologic and organ response and progression that can project overall survival are accelerating development of new therapies in clinical trials.[8] Nonetheless, AL amyloidosis remains a complex and a heterogeneous disease with a distinct interplay of precursor amyloidogenic light-chain production and vital organ dysfunction.

Currently, treatment of newly diagnosed patients with AL amyloidosis focuses on bortezomib-based regimens or high-dose melphalan and stem cell transplantation (SCT) for selected, eligible patients.[9,10] Novel agents such as novel proteasome inhibitors,[11] third-generation immunomodulatory agents,[12,13] and monoclonal antibodies to plasma cells[14,15] are being examined in clinical trials for patients with relapsed AL amyloidosis.

Little is known and available on outcome, presentation, pattern of relapse, and prognosis of patients with relapsed AL amyloidosis after an initial treatment.[16] This is particularly important as relapsed and refractory patients are selected for a good outcome and survival. More importantly, there is lack of consensus about when reinstitution of chemotherapy directed toward plasma cell dyscrasia should occur after an initial therapy and an initial hematologic response.

Timing of treatment of AL amyloidosis at relapse is of utmost relevance because of (1) a lag between hematologic progression and organ progression leading to overtreatment too early in the course of disease relapse, (2) health-related quality of life (HRQoL) due to treatment regimens vs organ dysfunction, and (3) pharmacoeconomics of the proposed novel agents that possibly could be delayed until organ dysfunction occurs.

There is ample evidence in the literature, albeit subtle, to support a delay in instituting treatment at the time of hematologic relapse for AL amyloidosis until symptoms of organ dysfunction occur. I will make this argument using published studies to convince the readers and focus on the 3 previously noted points.

Second-line treatment after initial SCT regimen

Currently, there are few studies reported with patterns of relapse after an initial treatment of high-dose melphalan and SCT in AL amyloidosis. We, at Boston University, reported on 647 patients with AL amyloidosis treated with SCT from 1994 to 2016 with hematologic relapse rate of 38.5% (n = 82/213).[17] The median time to hematologic relapse was 4.32 years (range, 1.4-21.5), and 13 of the 82 relapsed patients (15.9%) were determined to have a biochemical relapse only, based on abnormal results of a serum free light-chain assay or reappearance of a monoclonal gammopathy on serum or urine immunofixation electrophoreses, without evidence of organ disease progression. Given their overall end-organ stability, these patients with biochemical relapse did not require any additional anti–plasma cell therapy at a median follow-up of 6.53 years. Two of the patients with biochemical relapse died during the study period of other causes with no evidence of progressive organ disease due to AL amyloidosis. It is worth noting from this study that 16% of the patients with hematologic relapse did not have organ progression or the need for additional treatment at a median follow-up of 6.53 years, and even more importantly, 2 of these patients died of other causes.

Other studies have reported an event-free survival (defined as death or time to start a second line of therapy) of ~2 to 4 years in patients undergoing SCT for AL amyloidosis independent of hematologic response, which is quite prolonged.[18,19] These studies did not distinguish between hematologic and organ progression as criteria for initiation of second-line therapy.

A recent study from the Mayo Clinic delineated the timing of initiation of second-line therapy in 235 patients with AL amyloidosis after SCT from 1996 to 2014.[20] Of these 235 patients, 23% had hematologic progression or relapse without signs of organ progression. At the time of starting second-line therapy, only 63% of all patients met criteria for organ progression, and of note, 37% did not meet criteria for organ progression. In an effort to determine the timing between the earliest signs of hematologic relapse and organ progression, subset analysis demonstrated that the median time from "subtle" hematologic relapse to organ progression was 14 months, and only 25% of patients had organ progression at 5 months. It was also noted that patients with subtle hematologic relapse from very good partial response (VGPR) after SCT has a median of 2 years before evidence of organ progression, in contrast to those patients who achieved a less than VGPR after SCT. Importantly, organ progression could occur as late as 8.3 years (100 months) after hematologic relapse. Therefore, this group of patients could avoid treatment and its side effects (financial and medical) for all the years prior to organ progression and symptoms associated with organ dysfunction.

Second-line treatment after initial non-SCT regimens

The Pavia group recently reported on the outcome, variables leading to initiation of second-line therapy, and variables predicting survival after rescue treatment in 259 patients with AL amyloidosis who responded to nontransplant treatment regimens.[21] A definition of high-risk dFLC (difference between involved minus uninvolved serum free light-chain) progression is derived from this study if all of the following criteria are met: an absolute value of dFLC of >20 mg/L, a dFLC level that is at least 20% of the baseline value, and a dFLC that is at least 50% higher than the nadir dFLC achieved after therapy. After a median follow-up of 41 months, 35% needed a second line of therapy; however, 65% of the patients did not require second-line therapy. It is crucial to know the outcome of these 65% (n = 167) patients without additional treatment. Furthermore, it is also mentioned that 16.3% (n = 15) experienced dFLC relapse prior to cardiac progression by a median of 6 months (range, 2-8). One of the limitations of this report was that the multivariate analysis was underpowered to clarify the interaction between high-risk dFLC progression and baseline characteristics like extent of response (less than VGPR) and baseline cardiac function (more than cardiac stage I).

HRQoL in AL amyloidosis after treatment

Overall, AL amyloidosis patients have broad HRQoL deficits across all areas of physical and mental functioning compared with the general population. Longitudinal analyses of HRQoL, as measured by the SF-36 Health Survey, in patients who received different types of treatment of AL amyloidosis were reported by the Boston University group.[22] Significant improvements in HRQoL were found among patients who received SCT, as measured by significant mean differences in pre- and posttreatment physical and mental component summary scores ($P < .05$ for all). In contrast, no significant improvements in HRQoL scores were observed among patients who received non-SCT chemotherapy regimens; however, a significant reduction in general health (40.0 vs 34.1, $P < .001$) occurred among these patients following treatment.

Furthermore, the risk of treatment-related toxicity may have implications for treatment decisions, adherence, and HRQoL. This point of argument emphasizes for delaying second-line treatments (usually non-SCT regimens) until it is absolutely necessary and indicated for organ progression.

Pharmacoeconomics

Although not often discussed and acknowledged, a pharmacoeconomic perspective of novel next-generation agents used in the treatment of relapsed AL amyloidosis poses a major and real challenge. These challenges are not unique to any disease but are amplified specifically if used in the setting of relapsed AL amyloidosis with hematologic relapse without organ progression or symptoms of organ progression. The modern treatment of AL amyloidosis is expensive. A recent retrospective observational study of adult patients with AL amyloidosis using the US Optum administrative claims data from 2008 to 2015[23] demonstrated that 44% and 17% received doublet and triplet therapies for relapsed AL amyloidosis; additionally, ~30% received proteasome inhibitor (PI)–based and immunomodulatory drug (IMiD)–based therapy, and surprisingly, 6% received a combination of PIs and IMiDs. The average monthly cost was $14 369 per patient for relapsed AL amyloidosis, including medical costs ($9441) and drug costs ($4928). The average 1-year, 2-year, and 3-year cumulative health care costs for relapsed AL amyloidosis were $139 143, $275 391, and $342 349, respectively. This is first and the only published study to examine treatment patterns and patient outcomes for this disease utilizing a real-world claims database.

I do not regret the advances that have occurred in the treatment of relapsed AL amyloidosis. I welcome and embrace them enthusiastically. These advances have changed the face of AL amyloidosis and brought hope and improved survival of this once-fatal disease; however, early use of these exorbitantly expensive drugs (lenalidomide costs $100 000 per year,[24] and daratumumab costs $200 000 per year) with many side effects that could affect HRQoL, without accurate rationale and without organ progression, should be cautiously challenged. The point is that these agents are going to be needed for treatment when organ progression occurs, and this delay would be favorable economically as well as from the point of view of HRQoL without changing the responses or survival.

Outside of a clinical trial setting, I prefer delaying initiation of treatment of AL amyloidosis at hematologic relapse, except in selected high-risk patients in whom rapid cardiac progression is eminent. On this point, proponents of both early and delayed treatment when organ progression occurs for relapsed AL amyloidosis can agree.

Authorship

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