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VIEWPOINT

Call for New Therapies in Heart Failure

How Cardiology Can Learn From Oncology

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It's the treatment, stupid.
—Analogous to James Carville's statement on presidential re-election campaigns

Cardiologists and oncologists often differ in their treatment approach. This is illustrated in the management of light chain cardiac amyloidosis (also known as AL cardiac amyloidosis) compared with nonamyloid heart disease. Light chain cardiac amyloidosis differs from other forms of heart failure in that it is a rare disease with an incidence of ~1 patient per 100,000 and a prevalence of <10,000 U.S. individuals (1). Light chain amyloidosis is clinically heterogeneous and is a highly malignant disorder with extremely poor outcomes, especially among patients with advanced phenotypes whose survival is measured in weeks to months. The mortality in amyloidosis is almost always the result of cardiac involvement (2), with rising levels of natriuretic peptides accompanying progressive pump failure that can often culminate in electromechanical dissociation (3). The therapies shown to favorably affect outcomes in heart failure with reduced ejection fraction (HFrEF)—beta-blockers and renin-angiotensin system antagonists—are poorly tolerated in patients with AL cardiac amyloidosis and may even increase mortality.

Natriuretic peptides have been used widely by clinicians, especially heart failure specialists, in diagnostic testing to confirm heart failure as the cause of unexplained dyspnea and to determine prognosis in patients with HFrEF and heart failure with preserved ejection fraction (HFpEF). The widespread use of these peptides has occurred to the chagrin of esteemed experts in heart failure (4), whose view is supported by the neutral results of clinical trials using natriuretic peptides to guide management of patients with HFrEF (5). Indeed, there are many examples of discordance between the favorable effects of a heart failure therapy on natriuretic peptides and the lack of effect on "hard" outcomes (6). This discordance has led regulators such as the Food and Drug Administration to note appropriately that natriuretic peptides in heart failure do not meet the criterion for a surrogate endpoint, when a relationship with real outcomes is so reliably demonstrated that we can make decisions as confidently as—and perhaps much more feasibly than—the clinical outcomes of interest.

Light chains are toxic to cardiomyocytes (7); thus there is a tight link between the production of natriuretic peptides by cardiomyocytes in the setting of toxic free light chains. Stressed cardiomyocytes activate the p38 MAPK signaling pathway, which induces transcriptional up-regulation of the BNP gene (8). Thus, in AL cardiac amyloidosis, the levels of natriuretic peptides reflect the level of insult by light chain species to ventricular cardiomyocytes. Natriuretic peptides in AL cardiac amyloidosis do not decline significantly in the absence of a hematologic response, which is defined by a lowering of light chains, but they do so only *after* light chain levels fall with anti-plasma cell therapy. This finding is in contrast to natriuretic peptide responses in non-AL amyloid heart failure, in which multiple mechanisms, including but not limited to mechanical strain, neurohumoral factors, extracardiac conditions (anemia and obesity), and altered clearance, contribute to natriuretic peptide levels. In nonamyloid heart failure, natriuretic peptides are compensatory

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responses promoting vasodilation and improvement of fluid homeostasis. Simplistically, patients with AL cardiac amyloidosis die of progressive pump failure with concomitant relentless increases in natriuretic peptides that are reflective of the toxic-infiltrative cardiomyopathy.

Data on baseline natriuretic peptide levels in patients with AL cardiac amyloidosis have demonstrated robust predictive ability. N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels consistently reflect cardiac function and predict survival in patients with AL amyloidosis (9). Similarly, during treatment trials using various anti-plasma cell therapies, the NT-proBNP response, defined as a decrease in NT-proBNP of >30% and >300 ng/l (0.30 ng/ml or 35.4 pmol/l) in evaluable patients (those whose baseline NT-proBNP levels were ≥650 ng/l (0.65 ng/ml or 76.7 pmol/l), predicted clinical outcome and survival (10). Although these analyses were limited by their retrospective nature, prospective data have suggested similar predictive capacity (9).

So why do natriuretic peptides work in light chain amyloidosis and not in heart failure more generally? Possibly because our hematologic colleagues have a large and growing repertoire of therapies aimed at stopping the production of toxic light chains by rogue plasma cells. Their array of therapies incudes chemotherapies and autologous stem cell transplantation, as well as steroids, immunomodulatory drugs, proteasome inhibitors, alkylating agents, and now, monoclonal antibodies. Oncologists initiate treatment at high doses, expecting toxicity. And what do our hematology and oncology colleagues do if the patient with light chain cardiac amyloidosis does not achieve a hematologic response? They switch therapies, early and often, using an alternative pharmacological approach to shut off the production of toxic light chains by monoclonal plasma cells. Heart failure specialists use drugs at submaximal (and often subtherapeutic) dosages and increase the dose into the therapeutic range only when forced to by the patient's condition. What do we heart failure specialists do for patients with nonamyloid heart failure in response to a rising natriuretic peptide or levels that stubbornly will not budge? We use the same medications with the same mechanism of action but in an "intensified" fashion. My "oncological envy" is rooted in my desire to help my patients and by the observation that without new therapies guided by a basic understanding of the pathophysiological mechanisms that drive non-AL amyloid heart failure, biomarkers will not work. We need newer therapies and to administer them at optimal doses, not more biomarkers.

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