Brain Natriuretic Peptide: Potential Adjunct for Cardiac Risk Assessment and Management During Treatment With Experimental Anticancer Agents

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INTRODUCTION

A serum biomarker for monitoring myocardial dysfunction could potentially serve as a valuable adjunct to risk assessment and management when the biomarker is applied during the clinical development of cancer treatments. We explored the potential utility of serum brain natriuretic peptide (BNP), a hormone secreted predominantly by the ventricles in response to increased intracardiac pressure. In diverse clinical settings, elevated BNP has been reported to be a sensitive biomarker for the early (subclinical) diagnosis of congestive heart failure (CHF).¹ In the setting of a phase 1 study of an experimental agent for patients with advanced malignancies, we describe 3 cases in which serum BNP presented reliable information about left ventricular (LV) function, independent from or complementary to the results of conventional echocardiography (echo) or radio-nuclide multigated acquisition scan (MuGA).

An experimental, targeted kinase inhibitor was administered orally by continuous daily dosing in a phase 1 study. Clinical risk of LV dysfunction was not suggested by prior toxicology studies. Left ventricular ejection fraction (LVEF) was assessed by MuGA or echo, required at baseline and serially during the study. Serum BNP was also measured serially with exploratory intent. In each case, kidney and liver function tests were not significantly abnormal (common terminology criteria for adverse events [CTCAE] grade ≤ 1) throughout the treatment period. A brief description of each case is provided.

CASE STUDIES

Case 1

A 69-year-old female with metastatic breast cancer and a history of subclinical anthracycline-induced LV dysfunction was hospitalized for clinical CHF after receiving an investigational agent for 20 days. The patient satisfied eligi-

bility criteria, which excluded any clinical evidence of CHF. At baseline in the month preceding the study, the patient had acceptable LV function measured by echo and MuGA (LVEF = 35%-52%). The baseline BNP was significantly elevated to 787 pg/mL (reference upper limit < 100 pg/mL), but this laboratory finding was exploratory and not designed to affect eligibility for the protocol. After initial clinical diagnosis of LV dysfunction, repeat echo demonstrated LVEF decline to 15% to 20%. The CHF responded to diuresis and thoracentesis and, because a causal relationship could not be excluded, the experimental anticancer drug was permanently discontinued.

Case 2

An 85-year-old female with metastatic melanoma and no prior cardiac history or anthracycline exposure developed clinical CHF, diagnosed after 5 months of treatment with an investigational agent. A durable partial response to the agent was observed during the study. Baseline BNP was mildly elevated to 158 pg/mL. Serial BNPs on study demonstrated a stepwise increase to 1277 pg/mL, but these laboratory findings were exploratory and not designed to affect dosing in the protocol. A MuGA scan demonstrated reduced LVEF from baseline (68%) to 46%, although this was a relatively delayed finding. Although the patient achieved a durable response, the experimental drug was permanently stopped because of the clinically important CHF.

Case 3

A 52-year-old female with metastatic melanoma received multiple prior therapies, including interferon, vaccine, temozolomide, and high-dose interleukin-2. The patient also had history of stage 1 breast cancer, leading to adjuvant therapy with doxorubicin (cumulative dose 300 mg/m²). The baseline LVEF was 53% (by MuGA), and the BNP was normal. Two months after initiation of the investigational agent for the melanoma, routine MuGA showed an asymptomatic LVEF decline to 38%, a CTCAE grade 3 adverse event that would typically require discontinuation of the study drug. However, serial BNP values remained in the reference range. A cardiology consult was obtained. In contrast to MuGA, echo demonstrated normal LVEF (62%), enhanced after exercise to 68% without wall motion abnormality,

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and a stress test demonstrated normal exercise response. The cardiologist concluded that the patient had normal LV function and that the single LVEF of 38% by MuGA was spurious. These analyses enabled the patient to remain in the study.

DISCUSSION

These cases illustrate the difficulties in monitoring LV function using conventional echo or MuGA, and the potential value of serial BNP to complement or replace these more cumbersome imaging modalities.

In the first case, although baseline LVEF was normal, the patient developed worsening CHF only 20 days after initiating an experimental agent. In retrospect, the baseline BNP of 787 pg/mL likely indicated emergent LV dysfunction even with the acceptable LVEF measured by imaging technique. In future studies when the potential for treatment-emergent LV dysfunction is a concern, significantly elevated BNP at baseline may be a reasonable eligibility restriction. Alternatively, elevated BNP may be considered a stratification factor and/or a practical marker to guide the frequency and scope of further cardiac monitoring.

In the second case, BNP trended upward during study participation and, in retrospect, may have served as an early signal for the subsequent clinical CHF. Early detection of the subclinical BNP elevations could have enabled the continuation of the study drug following a dosing holiday or dose reduction, instead of the treatment discontinuation because of overt CHF. Unfortunately, this patient had to be withdrawn from the study drug, which was apparently providing durable disease control.

The third case illustrates the inherent difficulties in risk assessment by serial LVEF evaluations on a prespecified schedule in asymptomatic patients. Estimates of LVEF may vary $\pm 3\%$ to 5% in the same individual. Underlying chronic obstructive lung disease (for echo), high background counts (for MuGA), and other patient or technical factors may render assessments of LV function difficult and potentially inaccurate. BNP serves as an independent and easily measurable marker of left ventricular pressure overload. In this case, reduced LVEF coupled with a normal BNP prompted further cardiac investigations, which eventually confirmed normal left ventricular function. This case supports an algorithm in which a single decline in LVEF and/or elevated BNP, detected by serial monitoring in a patient without other signs or symptoms of left ventricular dysfunction, prompts evaluation by a cardiologist or other qualified person, prior to the decision to permanently discontinue protocol therapy. Such a risk management strategy, while ensuring the safety of study subjects, may also enable continued patient access to promising anticancer agents.

It is not unusual to see LVEF declines in phase 1 and 2 studies conducted in adults with advanced malignancies. Disease-related comorbidities and prior cardiotoxic treatments often confound MuGA and echo evaluations.² Likewise, BNP can be affected by multiple confounders, including acute pulmonary embolus, pulmonary hypertension, and renal failure. The analysis of adverse events can be especially challenging with some new targeted agents if they are associated with signs or symptoms associated with left ventricular dysfunction, specifically fluid retention, peripheral edema, and fatigue.³ While echo and MuGA are both subject to technical limitations,⁴ our experience and the experience of others⁵ support further investigations of serial BNP monitoring. Although BNP reference ranges and levels of concern have been described in other populations, the levels of concern and variability have not been well defined in patients with cancer receiving investigational therapy. Until more data become available in this setting, safety monitoring may be focused on following upward trends in BNP over time. Last, to improve confidence about BNP changes in this treatment setting, studies should be performed to determine whether investigational anticancer agents can modulate BNP protein expression, unrelated to adverse effects on cardiac function, given the precedent for this type of effect on serum biomarkers in other cancer treatment settings.⁶ With the growing recognition of cardiac morbidity in the clinical development of anticancer agents,⁷ continued studies are warranted to evaluate the predictive accuracy of serum BNP in patients with advanced cancer and the potential utility of BNP as an independent or adjunctive cardiac safety biomarker.

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