Targeting BRAF in Multiple Myeloma

Elizabeth O’Donnell and Noopur S. Raje

Summary: In multiple myeloma, it is believed that multiple mutations in different pathways deregulate the intrinsic biology of the plasma cell, resulting in a genetically complex heterogeneous disease. Mutations in the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway have been identified and represent potential targets for therapy in this disease. BRAF, a serine/threonine kinase, has received considerable attention given the success of targeted therapy in malignant melanoma. Andrulis and colleagues report, for the first time, successful treatment of multiple myeloma with vemurafenib, a BRAF inhibitor, in a patient with a BRAF mutation. Cancer Discov. 3(8); 840–2. ©2013 AACR.

See related article by Andrulis et al., p. 862 [1].

Although multiple myeloma was once a uniformly fatal disease, changes in the treatment paradigm have led to significantly extended overall survivals. Over the last 10 years, the availability of effective new drugs with acceptable toxicity, such as immunomodulatory drugs and proteasome inhibitors, have modified the traditional treatment paradigms in patients with multiple myeloma, resulting in an improvement in the quality and the duration of life. Despite these advances, these therapies are nonspecific, with pleiotropic mechanisms of action that do not specifically target genetic mutations. This is due, in part, to the complex genetic architecture of the disease that has not, thus far, been amenable to targeted approaches. In this issue, Andrulis and colleagues (1) report, for the first time, successful treatment with vemurafenib, a BRAF inhibitor, in a patient with a BRAF mutation.

Although it is known that there are characteristic chromosomal translocations resulting in overexpression of genes by juxtaposition to the immunoglobulin heavy chain (IgH) locus, these abnormalities cannot fully account for the malignant transformation to multiple myeloma, as many are found in the premalignant disease state, or monoclonal gammopathy of undetermined significance. It is believed that the activation of pathways including NF-kB and the activation of MYC, FGFR3, KRAS, and NRAS could play an important role in malignant transformation (2). In a recent Nature review, Morgan and colleagues (3) tackled the multistep evolution of the normal, functional plasma cell to the mutated, clonal myeloma cell. Morgan and colleagues (3) postulate that this process occurs in a Darwinian fashion, with immortality arising through the acquisition of mutations that confer a survival advantage. They assert that multiple mutations in different pathways deregulate the intrinsic biology of the plasma cell, resulting in a genetically complex heterogeneous disease. These events may not be acquired in a linear fashion, but rather through branching, nonlinear pathways. To add to the complexity of this genetic makeup, there is evidence of intracellular heterogeneity within the plasma cell compartment.

Mutations and deregulation can occur through diverse pathways. Translocations that place oncogenes under the strong enhancers of the IgH loci lead to deregulation of the G1-S transition. Gains and losses of DNA cause copy number alterations that cause loss of cell-cycle regulators and are also critical to the evolution of the plasma cell clone. Hyperploidy, with an odd-number gain of chromosomes, is associated with increased gene expression and with activating mutations in driver oncogenes. Finally, genetic mutations of NRAS, KRAS, and BRAF can lead to deregulation of the ERK pathway. Though there are few recurrently mutated genes, several of those identified fall within common pathways. Specifically, mutations in NRAS, KRAS, and BRAF fall within the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway.

In 2011, Chapman and colleagues (4) published the results of genome sequencing for 38 patients with multiple myeloma. In nearly 50% of patients, mutations were found in genes involving RNA processing, protein translation, and the unfolded protein response. Notably, 16 of 38 patients had mutations affecting protein translocation and homeostasis highlighting these as therapeutic targets. Statistically significant protein-coding mutations identified included NRAS, KRAS, FAM46C, DIS3, TP53, CCND1, PNRC1, ALOX12B, HLA-A, and MAGED1. In addition, one patient had a BRAF kinase mutation (G469A), prompting genotyping of an additional 161 multiple myeloma samples for the 12 most common BRAF mutations. Seven additional patients (4%) were identified with BRAF mutations. This was the first report, albeit in a small percentage of patients, of a druggable mutation in multiple myeloma; however, little was known of its oncogenic potential. In their article in this issue, Andrulis and colleagues (1) have tried to probe the biology of the BRAF mutation in the context of myeloma patient samples.

BRAF, a serine/threonine kinase, has received considerable attention given the success of targeted therapy in malignant...
melanoma. BRAF is a RAF kinase, and, as such, is a component of the MAPK/ERK pathway, a signal transduction pathway that transmits mitogenic signals from activated cell surface growth factor receptors under normal physiologic conditions (Fig. 1). In 2002, the Sanger Institute identified four BRAF mutations, including V600E, which were capable of causing RAS-independent activation of ERK, MAP-ERK kinase (MEK)-dependent cell proliferation, and transformation of fibroblasts (5). BRAF mutation constitutively activates BRAF and downstream signal transduction in the MAPK pathway. Large panel searches for mutations in common cancers identified BRAF mutations in 40% to 60% of melanomas and 7% to 8% of all cancers (5). The MAPK pathway has been previously shown to play a significant role in multiple myeloma cell growth and proliferation (6). RAS mutations are seen in more than 20% of patients with multiple myeloma, and most recently we have confirmed this in patients with myeloma using SNaPshot analysis on bone marrow samples (7). Attempts at targeting the MAPK pathway are under way in multiple myeloma.

In 2010, Flaherty and colleagues (8) published the results of the phase I study of PLX4032 (vemurafenib), an oral inhibitor of BRAF, in patients with malignant melanoma with the V600E mutation and showed complete or partial tumor regression in the majority of patients. In the subsequent phase III trial, the overall response rate was 53%, with a median duration of response of 6.7 months and a median progression-free survival of 6.8 months. The median overall survival was 15.9 months (95% confidence interval, 11.6–18.3; ref. 9). Similarly, in a patient with hairy cell leukemia, Dietrich and colleagues (10) reported a case of complete remission in a patient with refractory disease. The success of BRAF inhibitors in melanoma and hairy cell leukemia is encouraging, but not uniform. For example, the preclinical trials of BRAF inhibitors in colorectal cancer have been disappointing thus far (11). To better address the efficacy of this class of drugs, large-scale investigation of BRAF inhibitors in BRAF-mutant tumors is under way, such as an ongoing open-label, phase II study of vemurafenib in patients with BRAF V600 mutation-positive cancers, referred to as the Basket study, which includes patients with myeloma (NCT01524978).

Here, Andrulis and colleagues (1) report success with vemurafenib in a patient with multiple myeloma who harbors a BRAF mutation. From samples of 379 patients with multiple myeloma they found mutations of the BRAF gene in seven patients (∼4% of all cases), with the BRAF V600E mutation identified in six of them. The other patient harbored a BRAF V600K mutation. The patient presented with a bone marrow plasma cell infiltration of 8% and presented with severe bone pain. The plasma cell fraction increased to 10% after only one cycle of treatment with vemurafenib, and a complete remission was achieved 3 months later. The patient remains in remission 9 months after the start of vemurafenib treatment.

Figure 1. Illustration of the MAPK/ERK pathway. In normal plasma cells, the NRAS–BRAF–MEK–ERK signaling cascade (left, blue) tightly regulates cellular functions such as growth, differentiation, and survival. In multiple myeloma (right, red), BRAF-mutant myelomas (∼4%) bypass activation by NRAS, leading to oncogenic signaling through the MAPK/ERK pathway that favors excessive growth and survival.
being the most common, confirming the reported incidence of BRAF mutations in multiple myeloma (4). Interestingly, four of the seven patients (57%) went on to develop extramedullary disease compared with 43 of 251 controls (17%; P = 0.02). Patients with the mutation also had a significantly shorter median survival of 45 months (range 6–54) versus 105 months (range 4–227; P = 0.04) in patients without the mutation. This seems to be in keeping with evidence in other tumors that BRAF mutations confer an adverse prognosis. In their study, one patient with refractory multiple myeloma with the BRAF V600E mutation achieved a stable and durable remission with continuous use of off-label vemurafenib.

Though the presence of activating mutations does not universally predict for clinical and therapeutic relevance, work by Andrilis and colleagues (1) provides further support for optimism about the role of BRAF inhibition in the treatment of BRAF-mutant tumors and a possible targeted therapy in the treatment of multiple myeloma. The correlation of the presence of this mutation in the context of extramedullary disease needs to be further studied, as this will provide a novel avenue of patient-specific personalized therapy in a population whose outcomes with current drugs are grim.

Disclosure of Potential Conflicts of Interest

N.S. Raje is a consultant/advisory board member of Roche. No potential conflicts of interest were disclosed by the other author.

Published online August 8, 2013.

REFERENCES

Targeting BRAF in Multiple Myeloma

Elizabeth O'Donnell and Noopur S. Raje


Updated version  
Access the most recent version of this article at:
http://cancerdiscovery.aacrjournals.org/content/3/8/840

Cited articles  
This article cites 10 articles, 3 of which you can access for free at:
http://cancerdiscovery.aacrjournals.org/content/3/8/840.full#ref-list-1

Citing articles  
This article has been cited by 3 HighWire-hosted articles. Access the articles at:
http://cancerdiscovery.aacrjournals.org/content/3/8/840.full#related-urls

E-mail alerts  
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.