Commentary

Molecular Cancer Therapeutics

Mitogen-Activated Protein Kinases Inhibitors: Potential Therapeutic Agents for Cancer Cachexia

Vickie E. Baracos

The MAPK kinases, MEK1 and MEK2, act downstream of RAS/RAF to induce ERK activation, thereby communicating input from growth factors to promote proliferation of tumor cells. Binimetinib (MEK162, ARRY-162) and selumetinib (AZD6244) are MEK inhibitors developed to treat various cancers. MEK inhibitors have recently been combined with other agents acting on AKT, PI3K, or cyclin-dependent kinases, to potentiate their antitumor action. In current clinical trials, the use of these agents is extensively focused on K-RAS–mutant tumors and/or patients whose tumors show evidence of MEK activation.

In 2012, Prado and colleagues (1) detected skeletal muscle anabolism as a side effect of therapy with the MEK inhibitor selumetinib in patients with cholangiocarcinoma. This effect was hypothesized because selumetinib had been shown to inhibit IL6 production and IL6 is considered one of the principal catabolic actors in skeletal muscle. In this single-arm phase II study of selumetinib, 84% of patients robustly gained muscle, with a mean overall gain of total lumbar muscle cross-sectional area of 13.6 cm^2/100 days (or about 2.3 kg on a whole-body basis). A comparison was made with a separate group of cholangiocarcinoma patients on standard therapies, and as expected, these were markedly catabolic, with overall muscle loss of −7.3 cm^2/100 days (∼1.2 kg).

For the moment, the above-mentioned clinical data are an isolated observation that remains to be evaluated in further trials. Of note, however, is that the increase in skeletal muscle mass with selumetinib was equal or better than that achieved using the most recent cachexia-targeted therapy to date (2). The possibility that MEK inhibitors cause increases in skeletal muscle mass could easily be tested within currently and recently conducted randomized clinical trials of this class of agent. This is made eminently possible by the reading of CT scans taken to follow tumor response, for the alternative purpose of detecting changes in skeletal muscle. In the meantime, two recent publications (3, 4) by groups in the United States and China take up the question of the anticachexia action of MEK inhibitors in animal models of cancer cachexia, revealing key mechanisms.

Quan-Jun and colleagues (4) studied the cachexia-inducing C26 colon adenocarcinoma (4). In this model, selumetinib inhibited loss of weight and of skeletal muscle when given early or after cachexia was already well advanced. Further evaluation of mechanisms established that proinflammatory cytokines, including Il6, were not modified by selumetinib treatment; rather, the effects on muscle were associated with decreased phosphorylation of ERK1/2, downregulation of sentinel ubiquitin ligases involved in muscle protein catabolism (MuRF and MaFBX), and increased anabolic signaling via the PI3K/AKT signal transduction pathway.

Talbert and colleagues (3) also used the cachexia-inducing C26 colon adenocarcinoma, as well as a subclone of C26 lacking cachexia-inducing activity. Animals bearing these tumors were treated with binimetinib, a second MEK inhibitor with anti-cachexia actions. With this agent, muscle mass and fiber size were increased, systemic Il6 production was decreased, and the effects on muscle were associated with decreased phosphorylation of ERK as well as downregulation of sentinel ubiquitin ligases as well as several autophagy-related genes.

Both selumetinib and binimetinib caused some decrease in the growth of C26, an effect that could be partially responsible for the anticachexia actions of these MEK inhibitors. However, additional studies in both articles show that the effects on muscle were independent of the effect of the MEK inhibitors on tumor growth. Talbert and colleagues' (3) use of the noncachexic subclone of C26 is particularly clear in this regard. In line with current clinical investigations of MEK inhibitors, Talbert and colleagues went on to combine binimetinib with the PI3K/Akt inhibitor buparlisib, with the intention of testing for antitumor and anticachexia action of the individual and combined therapies. The two agents given together showed a strong additive effect on tumor control, with prevention of weight loss and retention of skeletal muscle fiber cross-sectional area.

It is a frequent observation that during anticancer therapy, patients are rendered highly catabolic. The mean expected rate of muscle loss in healthy community–dwelling people in the same age group as typical cancer patients is approximately 0.3% to 0.5% per year. Profound muscle loss is observed during anticancer therapy, and the rate at which this occurs represents an acceleration of muscle wasting of 20- to 50-fold the rate expected during normal aging. For example, in patients receiving standard chemotherapy for colon cancer, rates of muscle loss were reported to be 6.1% during 3 months (5), equal to approximately 24% on an annual basis. With the high precision of CT, such losses have been documented in several cytotoxic chemotherapy regimens as well as targeted therapies. With anticancer therapies resulting in muscle loss in kilogram quantities, it is obvious that these treatments will result in a deterioration of the body condition, of the functionality, and of the performance status of the patient.

In the recent past, we have witnessed multiple thought-provoking new findings in animal models suggesting new pathways and mechanisms of cancer cachexia and potential therapeutic targets. However, for the most part, these remain to be validated in a clinical context. The tale of the MEK inhibitors and cancer cachexia shows promise in the sense that the first available findings were from a clinical investigation (1). The subsequent pursuit of those findings in an animal model (3, 4) corroborates

Department of Oncology, University of Alberta, Edmonton, Alberta, Canada.

Corresponding Author: Vickie E. Baracos, Department of Oncology, University of Alberta, 11560 University Avenue, Edmonton, AB T6G 1Z2, Canada. Phone: 780-432-8232; Fax: 780-432-8425; E-mail: Vickie.Baracos@albertahealthservices.ca

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and extends those findings. There would be great merit in investigating systematically the effects of existing and new antineoplastic agents for their effects on muscle. This can be easily, quickly, and rapidly accomplished using the CT scans taken for the purpose of disease response. Muscle loss or gain is precisely quantifiable, within an error term typically less than 1%. This knowledge on new cancer therapies going forward would allow us to determine which cancer therapies fit in the spectrum ranging from those resulting in acute severe muscle loss and others that might, like MEK inhibitors, express an anabolic effect on muscle.

I have previously argued (6) that cachexia and loss of skeletal muscle mass and function are not to be considered inevitable consequences of cancer and cancer treatment. Multiple lines of experimental and clinical evidence demonstrate that even in the presence of advanced malignancies, skeletal muscle anabolism is intact and can be activated, independent of tumor progression. Recent findings with MEK inhibitors raise a tantalizing possibility: of a combined cancer therapy and cachexia therapy, resulting in more effective tumor control along with net improvement in the muscle mass, functionality, and performance status of the patient. This will require much further research, but it is seems a plausible goal.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Prado CM, Bekaii-Saab T, Doyle LA, Shrestha S, Ghosh S, Baracos VE, et al. Skeletal muscle anabolism is a side effect of therapy with the MEK inhibitor: selumetinib in patients with cholangiocarcinoma. Br J Cancer 2012; 106:1583–6.
2. Temel JS, Abernethy AP, Currow DC, Friend J, Duus EM, Yan Y, et al. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. Lancet Oncol 2016;17:519–31.
3. Talbert EE, Yang J, Mace TA, Farren MR, Farris AB, Young GS, et al. Dual inhibition of MEK and PI3K/Akt rescues cancer cachexia through both tumor extrinsic and intrinsic activities. Mol Cancer Ther 2016;16:342–54.
4. Quan-Jun Y, Yan H, Yong-Long H, Li-Li W, Jie L, Jin-Lu H, et al. Selumetinib attenuate skeletal muscle wasting in murine cachexia model through ERK inhibition and AKT activation. Mol Cancer Ther 2016; 16:332–41.
5. Blauwhoff-Buskermolen S, Versteeg KS, de van derSchueren MA, den Braver NR, Berkhof J, Langius JA, et al. Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. J Clin Oncol 2016;34: 1339–44
6. Baracos VE. Skeletal muscle anabolism in patients with advanced cancer. Lancet Oncol 2015;16:13–4.