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SCIENCE BEHIND THE STUDY
Elizabeth G. Phimister, Ph.D., *Editor*

Cancer Cachexia and the Brain Stem

Vickie E. Baracos, Ph.D.

In this issue of the *Journal*, Groarke et al.[1] report the results of a phase 2 clinical trial of ponsegromab therapy (100, 200, or 400 mg every 4 weeks) for cancer cachexia in patients with elevated humoral levels of growth differentiation factor 15 (GDF-15), and the editorial by Laird and Skipworth[2] discusses the findings. The GDF-15 protein is a cytokine in the transforming growth factor β family; ponsegromab, a humanized monoclonal antibody (see Key Concepts), inhibits it. Safety and efficacy were shown in patients with lung, pancreatic, or colorectal cancers who received 400 mg of ponsegromab every 4 weeks. At the end of the 12-week treatment period, participants in the 400-mg group had gained a median of 2.81 kg more weight than those in the placebo group, and the increase in the lumbar skeletal muscle index was greater by 2.04 cm² per square meter than that in the placebo group. The treatment-related adverse effects were minimal.

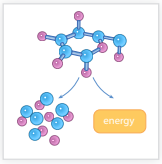
WHAT IS CANCER CACHEXIA?

Cancer cachexia is a syndrome defined by progressive weight loss in the presence of underlying malignant disease, which may culminate in extreme depletion of muscle and adipose tissue and, ultimately, death.[3] Its prevalence and severity varies across different types of cancer and among persons with the same type of cancer.

Cachexia is triggered by cancer, but tumor-induced immune activation and off-target effects of cancer therapies are also risk factors (Fig. 1). Patients with cachexia have reduced psychological, emotional, and social well-being related to their inadequate food intake, altered body image, and reduced physical function. Moreover, the condition incurs increased health care costs and confers a predisposition to cancer treatment–related complications and death. Despite renewed interest in cachexia therapeutics, treatment options are limited.[4]

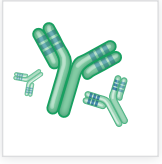
Clinical management of cachexia is defined by its two major etiologic components, reduced dietary intake and abnormal metabolism or catabolism.[3] Although nutritional deficit is not the sole culprit, severe nutrient deficiency is common.[5] Approximately a quarter of patients with advanced cancer consume less than 13 kcal per kilogram of body weight per day (equivalent to hypocaloric diets prescribed for intentional loss

Key Concepts



Catabolism

The enzymatic breakdown or degradation of large molecules, such as proteins, lipids, and carbohydrates into their constituent parts, such as amino acids, fatty acids, and glucose, respectively. Catabolic pathways release energy and usually generate ATP and reducing equivalents such as NADH. Conversely, anabolism is a constructive process, in which energy is used to synthesize macromolecules from simple molecules. Together, these metabolic processes maintain cellular homeostasis by balancing energy production and consumption.



Humanized monoclonal antibody

A therapeutic monoclonal antibody engineered to minimize human immune reactivity by grafting the complementarity-determining regions (CDRs) from a nonhuman (typically murine) antibody onto a human antibody framework. This approach preserves the specificity and affinity for antigen binding of the original antibody, while reducing immunogenicity. Humanized monoclonal antibodies are used in the treatment of cancer, autoimmune disorders, and infections.

Monoclonal antibody

An antibody produced by a B-cell clone that has been fused with a myeloma cell (to confer "immortality"). It has high affinity for a region (an epitope) of an antigen, such as a protein expressed by a parasite. Because of their high specificity and natural starting point, monoclonal antibodies usually have fewer off-target effects than small-molecule drugs in most patients. They can be produced on a large scale in bioreactors.

An expanded illustrated glossary is available at NEJM.org

of approximately 2.5 kg over a period of 30 days in patients with obesity).[5] Set against a mean (±SD) total energy expenditure of 29.7±6.3 kcal per kilogram per day,[6] inadequate food intake is an unquestionable cause of negative energy balance. Counseling patients to eat more energy-dense foods cannot fully reverse cachexia if symptoms such as lack of appetite and nausea remain ongoing deterrents to eating.

THE BRAIN STEM, ANOREXIA, SATIETY, NAUSEA, AND VOMITING

Several mechanisms that curtail food intake reside in the brain stem. Their physiological relevance is to avoid overfeeding (through response to overdistention of the gut and osmolar overload, for example), to halt the intake of toxic compounds and eject them (vomiting), and to condition aversion. Unlike the nuanced interplay of orexigenic and anorexigenic neurocircuits in the hypothalamus, which tailor nutrient influx during meals by balancing appetite and satiation, the functions vested in the brain stem are considered to be alarm responses that swiftly halt food intake.

On binding its receptor, which is expressed on neurons in the area postrema and nucleus of the solitary tract of the brain stem, GDF-15 induces anorexigenic and aversive responses and nausea.[7] GDF-15 is overexpressed by many tumors. It is also induced in nontumor tissues by cancer therapies, particularly cisplatin — a double setback. Through its effects on the gut and the chemoreceptor trigger zone of the brain stem, cisplatin is emetogenic. Its induction of GDF-15 synthesis increases levels of systemic GDF-15 and thus adds further impetus to nausea and vomiting. The most vulnerable patients may be those with the unfortunate combination of elevated circulating GDF-15 levels and concurrent emetogenic chemotherapy. Additional results implicate the brain stem and nausea in cachexia. For example, in a phase 3 trial, treatment with olanzapine (which suppresses nausea) resulted in a mean weight gain of 2.7 kg in patients with advanced lung and gastrointestinal cancers and cachexia.[8] A comprehensive understanding of how cancer affects the brain stem is still lacking. Indeed, the discovery of pathways of satiety and aversion in the brain stem continues apace.[9] For example, a recent study supports an anorexigenic action of interleukin-6 in the area postrema.[10]

WHAT'S NEXT?

Recognition that failed food intake is a key driver of cachexia is long overdue. Beyond the results of the trial by Groarke et al., we need to know the durability of the effects of ponsegromab beyond 12 weeks and the most effective timing of treatment and its efficacy. The lack of data on the natural history and epidemiology of cachexia and on levels of GDF-15 in patients with cancer cachexia limit the ability to target ponsegromab to the patients most likely to have a response. Other molecules that suppress feeding (e.g., interleukin-1β) may be concurrently present with GDF-15 or drive anorexia in distinct populations of patients.

The wealth of mature concepts and methods developed by researchers studying the neuroscience of obesity comprise a valuable toolkit for

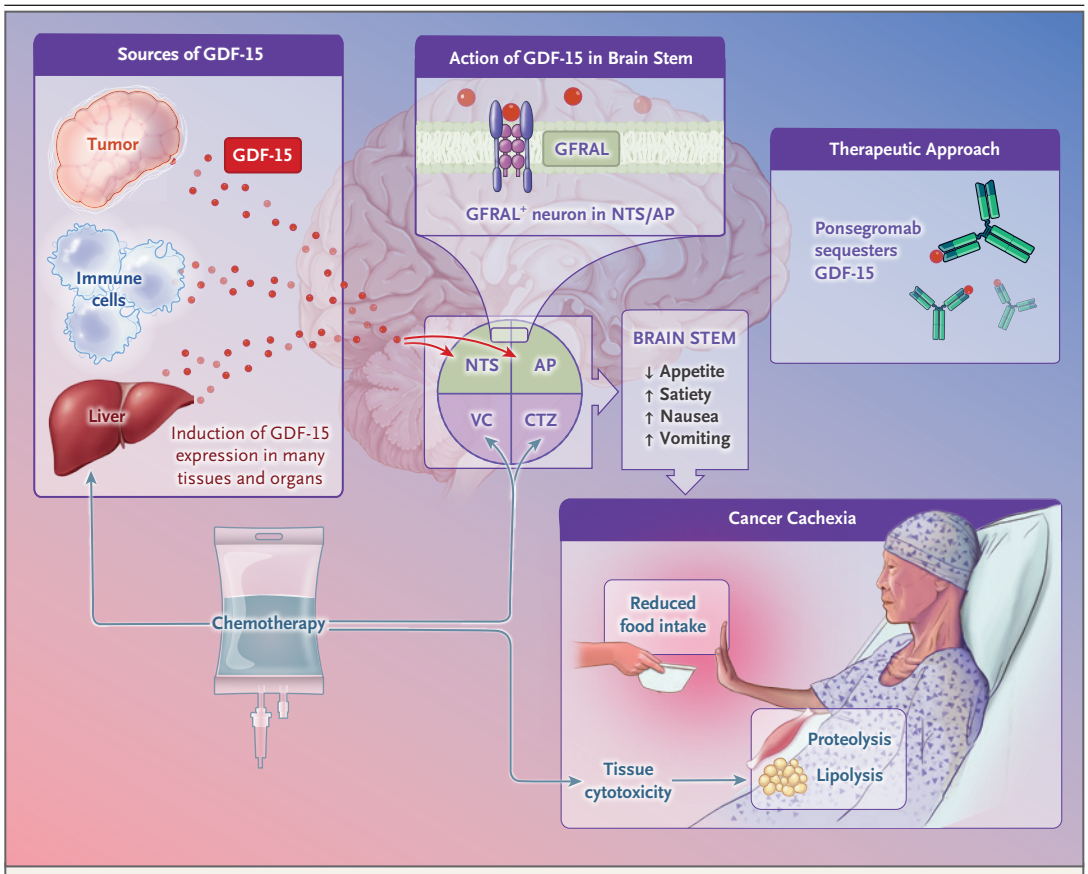


Figure 1. Ponsegromab, GDF-15, and Cancer Cachexia.

Cachexia is initiated by a complex mixture of tumor-derived factors and proinflammatory molecules generated by cross-talk between tumor cells and associated immune cells. These factors may elicit catabolism directly in the end organs of cachexia (skeletal muscle, adipose tissue, and heart) or do so through the central nervous system. Chemotherapy spurs on cachexia by the induction of nausea and vomiting and through toxic actions on muscle and fat cells. Multiple sources contribute to rising humoral levels of growth differentiation factor 15 (GDF-15), which is expressed by tumor cells, immune cells, and organs and tissues (liver, kidney, and muscle and adipose tissue) in response to chemotherapy. Key brain regions that regulate energy balance include the brain stem, hypothalamus, and reward system. Interconnected brain-stem regions include the area postrema (AP), nucleus tractus solitarius (NTS), chemoreceptor trigger zone (CTZ), and vomiting center (VC). GDF-15 exerts its action through a specific receptor (glial cell–derived neurotrophic factor family receptor α-like [GFRAL]) expressed by neurons of the AP and NTS, intersecting with chemotherapy-induced nausea (signaled directly on the CTZ as well as from the gastrointestinal tract via the vagus nerve; the latter is not shown).

cachexia researchers. The neurocircuitry that governs body weight consists of a complex, interconnected network, including the hypothalamus, cortical sites, reward centers, and the brain stem. Distinct neuronal populations interconnect brain regions by means of circulating hormones, nutrients, metabolites, and postprandial signals. The hypothalamus regulates appetite, satiation, metabolism, thirst, circadian rhythms, and multiple endocrine axes directly and indirectly: cancer-associated perturbation of the hypothalamus can have widespread consequences. One hypothalamic mechanism for excess satiety in cancer cachexia is postulated to involve activation of the anorexigenic melanocortin 4 receptor (MC4R).[11] Therapeutics can now be directed at this mechanism with the advent of small molecule receptor antagonists that can pass the blood–brain barrier, with a first-in-class compound (TCMCB07) presently being tested in a phase 1 study (ClinicalTrials.gov number, NCT05529849). Other pathways of neural regulation of feeding remain unexplored in cancer cachexia. The reward system has been extensively studied in

obesity, and because its physiological role is to motivate the ingestion of palatable calorically dense foods, perhaps it can be leveraged to help restore energy balance in patients with cancer.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Levofloxacin Preventive Therapy for Persons Exposed to MDR Tuberculosis

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The use of preventive tuberculosis treatment after *Mycobacterium tuberculosis* infection, historically with isoniazid and more recently with shorter-duration rifamycin regimens, is a core component of tuberculosis control in the United States and is increasingly being used in some tuberculosis-endemic areas.[1] However, multidrug-resistant (MDR) tuberculosis, which is caused by *M. tuberculosis* resistant to isoniazid and rifampin, threatens efforts to control tuberculosis. Worldwide, most initiatives to address MDR tuberculosis have focused on disease diagnosis and treatment, resulting in important successes in these areas.[2-5]

Less has been done in the domain of chemoprevention after exposure to a person with MDR tuberculosis, despite evidence from mathematical modeling that shows the potential importance of chemopreventive therapy to tuberculosis control.[6] The current World Health Organization recommendation that "in selected high-risk household contacts of patients with [MDR tuberculosis], preventive treatment may be considered based on individualized risk assessment and a sound clinical justification" is conditional because it is based on very-low-quality evidence.[7] The absence of clear guidance about the choice and duration of drug therapy in persons exposed to a person with MDR tuberculosis has resulted in poor uptake of this recommendation in most settings.

In this issue of the *Journal*, Fox et al.[8] and Hesseling et al.[9] provide solid evidence of a role for levofloxacin in the prevention of tuberculosis disease in persons with household exposure to an index patient with MDR tuberculosis. Both double-blind, randomized, controlled trials assessed the efficacy of levofloxacin, administered orally once daily for 6 months, as compared with placebo for the prevention of tuberculosis disease. The VQUIN MDR trial was conducted in Vietnam and enrolled mainly adults. The TB-CHAMP (Tuberculosis Child Multidrug-Resistant Preventive Therapy) trial was conducted in South Africa and enrolled children. In the VQUIN MDR trial, tuberculosis disease developed in 6 of 1023 participants assigned to receive levofloxacin and in