

# Anti-cachexia therapy should target metabolism, inflammatory cytokines, and androgens in hormone-independent cancers

Cancer cachexia is characterized by hypermetabolism in about 50% of the patients.<sup>1</sup> This increased energy expenditure leads to a negative energy balance and weight loss. It would appear that reducing hypermetabolism is one avenue to reduce weight loss induced by cancer. Additionally, from observational studies, it appears that interleukin-6 (IL-6) most likely secreted by the tumours is a causative factor in reduced muscle protein synthesis seen in cancer.<sup>2</sup> Thus, inhibiting the effects of IL-6 would be important to reduce cachexia directed at skeletal muscle in cancer. Another manifestation of cancer is reduced circulating testosterone concentrations.<sup>3</sup> Elevating testosterone back to normal circulating concentrations or above the patient's pre-cancer normal level with testosterone replacement therapy or elevating other androgens with other anabolic agents such as anabolic steroids would appear to be prudent for reducing the loss of lean body mass.<sup>4–6</sup> Obviously, you would only want to do this with cancers which were not hormone sensitive. With this three-pronged approach to reducing or stopping cancer cachexia, survival duration could be prolonged and other cancer therapies, such as chemotherapy, radiation therapy, and surgery, could be used during this 'extra' survival time to inhibit or remove the tumour and its negative effects.

Epinephrine stimulates mitochondrial respiration.<sup>7</sup> This at the whole body level would increase resting metabolic rate and energy expenditure via the beta-2 adrenoceptor. Blocking the effects of circulating epinephrine with selective beta-2 blockade with a drug such as propranolol (which blocks both B1 and B2 receptors) would seem to a prudent practice to reverse the hypermetabolism found in about half of cancer patients.<sup>1</sup>

The major source of the catabolic effect of a tumour on skeletal muscle appears to be through the elevation of the proinflammatory cytokine IL-6.<sup>2</sup> IL-6 has been shown to inhibit muscle protein synthesis in mouse model where IL-6 secretion was elevated in a genetic knockout model.<sup>2</sup>

The drug Sylvant (siltuximab) has been FDA approved for Idiopathic Multicentric Castleman disease and is antibody for IL-6, effectively negating the effects of IL-6 in the body. Therefore, the off-label use of siltuximab would appear a prudent practice for oncologists treating cancer cachexia.

The third intervention that would appear to reduce cancer cachexia and promote lean body mass retention in cancer cachexia would be the administration or rather replacement of androgens in individuals with cancer. Circulating testosterone concentrations have been shown to be hypogonadal in cachectic cancer patients.<sup>3</sup> Testosterone administration has been shown to promote lean body mass accrual in healthy volunteers.<sup>4</sup> Clearly, this could only be used in individuals with hormone-insensitive cancers and is contraindicated in prostate, breast, uterine, endometrial, cervical cancers and possibly others. This is the case for predominantly 'female cancers' because some of the testosterone is converted to oestrogen in a process called aromatization. Another approach would be to administer anabolic steroids which have the beneficial effects of testosterone and lack of secondary side effects (called androgenic effects) rather than administer testosterone.<sup>5,6</sup> Anabolic steroids which have been administered in other diseases<sup>5,6</sup> and that have high anabolic (muscle growth effect) and low androgenic effect (secondary sexual side effects) are nandrolone decanoate (an IM injectable) and oxandrolone (an oral). Obviously, liver function tests would be need to be closely monitored if oxandrolone was administered. Clearly, the doses of these three drugs would be need to be determined in cancer patients, but a possible strategy would be start out with small doses and increase weekly until therapeutic benefit to side effect ratio was optimal.

An additional intervention that would stimulate muscle protein synthesis and augment the effects of androgens on muscle protein accretion is progressive resistance exercise also known as resistance exercise. This brings up the question of how to measure efficacy. This is modality that

is proven but is a modality that requires the patient to be somewhat ambulatory.<sup>8</sup>

Measuring body composition over time requires possibly complex equipment; however, there are valid and reliable methodologies such as multifrequency bioelectrical impedance that can be done with the patient in bed.

To reiterate, reducing the hypermetabolism of cancer cachexia by administering propranolol, increasing the androgen concentration by administering testosterone, nandrolone decanoate, or oxandrolone and inhibiting the effects of IL-6 by administering siltuximab would be a three-pronged

approach that can be implemented by the oncologist and that can be efficacious by individualizing dosages and monitoring toxicology results such as liver function tests. These three drug classes are all FDA approved but could be used for this off-label pathology. Additionally, resistance exercise (weight training) can increase muscle mass in individuals undergoing bed rest.<sup>8</sup>

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