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PERSPECTIVE ARTICLE

Repurposing anabolic agents in cancer cachexia: A perspective

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Abstract

Cancer cachexia kills millions of people worldwide every decade. Attenuating or mitigating this muscle-wasting condition associated with cancer could significantly reduce cancer-related deaths. The drug development pipeline takes 10 – 15 years to complete in the United States. During this period, hundreds of thousands to millions worldwide die of cancer cachexia. Medicines already approved by the United States Food and Drug Administration that cause significant muscle mass gains in healthy individuals could be used "off-label" or "repurposed" in individuals who do not have androgen receptor-responsive cancers. These agents are testosterone and anabolic steroids. In individuals with androgen receptor-responsive tumors, repurposing anabolic agents (e.g., beta-2 adrenergic agonist albuterol), which increases muscle mass through different mechanisms than the androgen receptor, is warranted. New research suggests that phenotyping for the androgen receptor must be conducted individually, even for the same cancer. The utilization of these two types of anabolic agents – those that use the androgen receptor and those that do not – in appropriate clinical trials in cancer cachexia is also warranted.

Keywords: Cancer cachexia; Testosterone; Anabolic steroids; Beta-2 adrenergic agonists; Prostate cancer; Breast cancer; Androgen receptor

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1. Cancer cachexia: Prevalence and mortality

Cancers are the second leading cause of death in the United States (US), surpassed only by cardiovascular diseases. Approximately 50% of cancer patients suffer from cachexia or disease-related muscle wasting.[1] This definition of cachexia proposed by Evans *et al.*[2] is a 5% weight loss in 12 months with an underlying disease, without fluid loss, along with a loss of muscle mass with or without fat loss, and at least three of the following five criteria: (i) Decreased muscle strength, (ii) fatigue, (iii) anorexia, (iv) low fat-free mass index, and/or (v) abnormal biochemistry results (elevated C-reactive protein and/or interleukin-6, anemia, and/or low serum albumin). Different types of cancer, disease stages, and patient characteristics[2] influence the prevalence of cachexia. Cancer cachexia, as defined in clinical practice, varies significantly due to a lack of consensus among physicians and researchers worldwide. Multiple groups[2-4] have differing definitions of cachexia. However, regardless of the definition of cachexia, the primary concern should be the high mortality rates associated with this condition. One challenge in the early and accurate diagnosis of cancer cachexia is the difficulty in obtaining an early diagnosis of cancer itself. Additional limitations include the need for specific patient data, such

as strength measurements, which take time and are not routinely conducted by oncology teams.

Approximately 80% of all cancer mortalities are associated with highly cachectic cancers, such as pancreatic and non-small cell lung carcinoma. The prevalence of cachexia is greater in males, those with a lower body mass index, and if sarcopenia is present. The use of chemotherapy will also increase the prevalence of cachexia. In Europe, the US, and Japan, the 1-year mortality rate is 20 – 80%.[1] Given that about 50% of cancer patients suffer from cachexia and the 20 – 80% 1-year mortality rate in these developed areas, 10 – 40% of all cancer patients die of cachexia or cancer-related muscle wasting. Our focus should be on the number of cancer patients dying rather than solely on the prevalence of cachexia. A rough calculation based on cancer incidence data in Europe (2018), the US (2022), and Japan (2022) estimates that cancer cachexia is responsible for 391,000 – 1,356,400 deaths in Europe,[5] 238,019 – 952,076 deaths in the US,[1] and 100,516 – 402,060 deaths in Japan.[1] Even if the 50% prevalence rate of cancer cachexia is a liberal estimate, there are still at least 50,000 deaths from cancer cachexia in each of Europe, the US, and Japan, and this is not a trivial problem. Therefore, cancer cachexia attenuation and mitigation could save hundreds of thousands of lives in each of these three geographical locations. This is an urgent issue, and the repurposing of anabolic agents could help stop or at least reduce these high mortality rates. It should be noted that the diagnosis of cachexia is less important than treating it with anabolic agents. In no circumstances would an increase in muscle mass be detrimental to a cancer patient's health, Grip strength is highly inversely related to mortality in the elderly.[6] Hence, it is proposed that treating all cancer patients with an appropriate anabolic agent would increase life expectancy and reduce mortality rates. Anabolic steroids or testosterone in non-androgen receptor-responsive tumors, and albuterol or other non-androgen receptor-binding anabolics in androgen receptor-responsive tumors, should be considered the standard of care. In simple terms: treat the cancer cachexia and discontinue treatment during remission.

Anabolic therapies can and have been combined with chemotherapy and radiotherapy in important clinical trials. This is crucial, as chemotherapy has been demonstrated to reduce muscle mass.[7]

2. Pharmacodynamics explaining higher response to pharmacological doses than physiological doses of a drug

The physiological and pharmacological molecular mechanisms that result in higher pharmacological response to androgens compared to physiological doses are explained by the Michaelis–Menten kinetics associated with androgen/receptor interactions, such as the substrate concentration that causes 1 - half maximum reaction velocity (K_m) and maximal reaction velocity (V_{max}). K_m is derived from the middle of a hyperbolic curve, in which the concentration at 50% V_{max} elicits a linear response but at half-maximal. Increasing the dosage increases the rate of receptor binding linearly until it reaches the maximal binding rate (i.e., the V_{max}), which is the plateau of the hyperbolic curve.[8]

3. Mechanism of action of androgens in skeletal muscle through the androgen receptor

Androgens bind to the androgen receptor in the cytoplasm of the cell; this complex then migrates into the nucleus and binds to DNA, inducing gene transcription in skeletal muscles. Two notable deviations from the strict ligand (steroid) specificity occur when dosages shift from physiological to pharmacological levels, as observed by Pihlajamaa *et al.*[9]: (i) Pharmacological dosages produce more pronounced effects than physiological dosages, and (ii) different steroid structures exhibit varying affinities for the androgen receptor, with some binding more effectively than others.[9] This prompts the research question: Can epigenetics affect the response to androgens? Through both extranuclear and nuclear mechanisms, androgens can activate or repress histone activity, thereby influencing protein signaling.[10]

4. Mechanisms of action of androgens in breast tissue, prostate tissue, and other tissues during metastatic cancer

Steroid-hormone-receptor interactions recruit signaling and/or scaffold proteins, stimulating flux through various pathways that promote cancer cell proliferation, survival, and migration for tissue invasion.[11] Several scaffold proteins[12] are as follows: (i) Steroid receptor co-activator-1 (Src)[13] is involved in androgen-induced prostate cancer cell proliferation; (ii) integrins are membrane linkers across cell membranes that interact with the cytoskeleton and extracellular matrix to induce metastasis and cell invasion;[14] (iii) filamin A is a cytoskeleton protein that regulates androgen responsiveness through the androgen receptor and downregulates androgen receptor function;[15] (iv) PI3K is a signaling kinase (phosphorylates) that is essential in insulin-signaling;[16] and (v) P130 Cas is involved in cell migration, apoptosis, and cell cycle control.[17] According to Giovannelli *et al.*,[11] the interaction of classical ligand-bound steroid receptors with scaffold and/or signaling proteins regulates cellular processes,

such as chromatin remodeling, cell cycle proliferation, and cell migration. In addition, the exclusion of nuclear steroid receptors and relegation to the cytoplasm may be controlled by the interaction of these receptors and signaling and/or scaffold proteins. Androgens can activate or repress histone activity through extranuclear and nuclear mechanisms, thereby influencing protein signaling and exerting epigenetic effects.[10] Androgens exert similar effects in androgen receptor-positive tissues (prostate, breast, and skeletal muscle); these effects are generally anabolic and/or proliferative responses.

Another factor that affects the anabolic response to androgens is the tumor microenvironment. For example, tumor necrosis factor-alpha in the tumor microenvironment is a negative regulator of protein metabolism[18] that promotes degradation and reduces protein synthesis in muscles, suggesting competing influences on the anabolic response to androgens.

Isomers with the same chemical formula but different atomic arrangements can affect receptor binding due to altered specificity. For example, glucose binds to its receptor with much more binding affinity than fructose. Despite having the same chemical formula ($C_6H_{12}O_6$), the fructose isomer has a lower binding affinity toward glucose receptors.

5. Repurposing of anabolic agents

If the high mortality rates are not compelling enough, the lengthy time required to bring a new drug to market, the immense cost of this process, and the countless lives lost during this period should be truly eye-opening. The entire process from drug discovery to full Food and Drug Administration (FDA) approval, inclusive of pre-clinical and clinical trials, takes approximately 10 – 15 years. At a moderate mortality rate of 500,000/year, a 10-year FDA approval process would result in 5 million deaths in the US. While repurposing anabolic agents may not save all lives, bodybuilders allegedly taking these agents may gain 5 – 10 kg of muscle with resistance training[19] in a short period. Bhasin *et al.*[19] reported that healthy men receiving 600 mg/week of testosterone enanthate, combined with resistance training, gained 6.1 kg of fat-free mass in 10 weeks. This accrual of skeletal muscle tissue in cancer patients would allow time for other oncology practices, such as chemotherapy, radiotherapy, surgery, and immunotherapy, to take effect and eliminate tumor-derived cancer. Cancer patients who die from cachexia are often believed to succumb to respiratory muscle atrophy and failure. Considering the time, cost, and lives lost, it is imperative to repurpose anabolic agents, such as testosterone and steroids. In the first clinical trial investigating the effects of anabolic agents on cancer cachexia, Wright *et al.*[20] reported that the administration of 100 mg of testosterone to cervical and head and neck cancer patients undergoing chemotherapy and chemoradiation resulted in a 3.2% increase in muscle mass in the testosterone group and a 3.3% decline in the placebo group after 7 weeks of administration. There was no improvement in muscle strength, physical performance, and survival, but there was an improvement in the quality of life. Limitations of this study include the low dose of testosterone administered in a life-threatening situation and the relatively short duration of administration. Given the high risk of mortality in these patients, this should encourage physicians and scientists to adopt more aggressive approaches. The likelihood of liver problems is low with injectable testosterone or anabolic steroids. In addition, the use of anabolic steroids (e.g., nandrolone decanoate) in high doses would be safer than high doses of testosterone due to the relative androgenicity between the two agents. The higher dose of testosterone (600 mg/week) used in normal non-cancer patients by Bhasin *et al.*[19] resulted in a 6.1 kg increase in lean body mass in healthy individuals. Moreover, the typical testosterone cycle for a powerlifter involves 1 – 2 g/week, along with 50 – 100 mg/day of Dianabol or Anadrol for 8 – 16 weeks. These strength athletes live healthily and do not experience immediate mortality after completing the cycle.[21]

The anabolic response would be greater in a cancer patient depleted of skeletal muscle compared to healthy controls, due to a potential ceiling effect. Based on my understanding of floor and ceiling effects, anabolic agents should be used at all stages of cancer. Early use could prevent a significant decline in muscle mass, and theoretically, the more negative the nitrogen balance, the greater the corrective effect anabolic agents could have. Notably, high-energy (kcals) and protein/amino-acid intake, either enterally or parenterally, should accompany high-dose testosterone or anabolic steroid administration in such a situation.

6. Androgen sensitivity or androgen receptor presence in different tumor types

The presence of androgen receptors in tumors suggests that these tumors will grow when stimulated by androgens. Therefore, for certain cancers, androgen receptor stimulation using testosterone, anabolic steroids, and other androgens is not an option. One alternative is to treat androgen-sensitive tumors with anabolic agents that do not stimulate the androgen receptor.

According to Viehweger *et al.*[22] androgen receptor-positivity, measured through immunohistochemistry, is similar in testicular and ovarian stromal tumors as it is in

prostate tumors. Moreover, breast, renal, and urothelial cancers have high androgen receptor expression. However, androgen receptor expression varies across different tumor types, with an approximate expression of 25 – 75% in breast cancer.

The expression of the androgen receptor is not homogeneous for all tumors of the same type. Some patients are androgen receptor-positive, whereas others are not for a given tumor type. Breast cancer can be androgen receptor-positive or androgen receptor-negative, suggesting that the same type of cancer may have tumors that are proliferative to androgens, whereas others are not responsive. Individual testing of biopsy samples from the tumor with immunohistochemistry could help with this approach. For androgen receptor-negative tumors, androgens may be used. In contrast, for androgen receptor-positive tumors, non-androgenic anabolics such as albuterol could be more appropriate.

7. Discussion

Cancer cachexia affects many cancer patients, and developing new drugs for this condition is a long and costly process, with an estimated 5 million cancer patients potentially dying in the meantime. Repurposing already approved anabolic agents, such as testosterone and anabolic steroids, could substantially reduce the mortality rate of cancer cachexia.

One potential treatment that required rigorous clinical trials in androgen receptor-positive cancers is albuterol. The rationale for using albuterol in these cancers is that androgens can stimulate tumor proliferation. Uc *et al*.[23] previously reported in Parkinson's patients that albuterol was anabolic to skeletal muscle. In a previous study,[23] a 5.3% increase in lower limb muscle mass (quadriceps femoris) and a 9.5% increase in whole body lean body mass were observed after 14 weeks of albuterol administration (16 mg/day). Lambert *et al*. (unpublished data) observed a 90% increase in skeletal muscle protein synthesis (in the vastus lateralis skeletal muscle) as a result of 16 mg/day albuterol administration for 10 days in healthy elderly individuals. Future clinical trials involving albuterol in androgen receptor-positive cancer patients are warranted to help attenuate and mitigate death from cancer cachexia. The mechanism of action of albuterol is likely due to the increase in cAMP intracellularly through stimulation of the beta-2 adrenergic receptor, thereby inducing the phosphorylation of various kinases within the skeletal muscle cell.[24] The exact mechanism by which albuterol stimulates skeletal muscle protein synthesis remains unknown, warranting further studies. Other signaling pathways for beta-2 adrenergic agonists include tyrosine kinases, which can phosphorylate the beta-2 adrenergic receptor at multiple sites, deactivating it through insulin. Insulin-like growth factor (IGF-1) can also phosphorylate and deactivate the receptor. In addition, eukaryotic initiation factor 2B activates the beta-2 adrenergic receptor, whereas arrestin is involved in decreasing receptor activation and signaling. There may be other mechanisms of action for beta-2 adrenergic agonists in the skeletal muscle and interactions with other pathways, but these have yet to be elucidated. A book chapter published nearly two decades ago[25] suggested that IGF-II could mediate beta-2 adrenergic agonist activation in skeletal muscle.

8. Conclusion

Testosterone, anabolic steroids, and albuterol are promising options to reduce the loss of ~5 million lives over the next 10 – 15 years. These agents, though not extensively studied in cancer cachexia, offer hope if used properly and for sufficient duration.

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Conflict of interest

The author declares he has no competing interests.

Author contributions

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Ethics approval and consent to participate

Approval for Albuterol study was obtained from the local ethics commitee.

Consent for publication

Not applicable.

Availability of data

Data are available from the corresponding author upon reasonable request.

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