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ROLE OF ANABOLIC AGENTS IN CURTAILING THE MORBIDITY OF CANCER CACHEXIA

Oncology

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ABSTRACT

Cancer cachexia is a multifactorial syndrome with an ongoing loss of skeletal muscle mass (± loss of fat mass) associated with functional impairment. Standard treatment for management of cachexia is yet to approve, thus the aim of this review is to determine the role of anabolic agents in cancer cachexia patients. Literature was searched for testosterone or its derivatives e.g. Oxandrolone and nandrolone and newer anabolic agent enobosarm and their impact and safety profile was analyzed.

More studies are needed for anabolic steroids with larger group of patients and enobosam is showing promising results with good safety profile but still lacking evidence to make it a standard treatment.

KEYWORDS

Cancer cachexia, Weight loss, enobosarm

INTRODUCTION

Cancer cachexia is a multifactorial syndrome which is defined by Fearon K et al as an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that can't be fully reversed by conventional nutritional support and leads to progressive functional impairment (1). `11

Although in cancer, disease control is achieved with state of art treatment modalities i.e. surgery, chemotherapy and/or radiotherapy but these interventions along with the disease itself play a role in causation of cancer cachexia, thus forming a vicious circle. Cancer cachexia is characterized by marked loss of body weight, anorexia, wasting, systemic inflammation and anemia; however, variable extent of these factors is seen (2, 3). Diagnostic criterion for cachexia are weight loss greater than 5%, or weight loss greater than 2% in individuals with body-mass index <20 kg/m² or appendicular skeletal muscle index consistent with sarcopenia. However there is no clear consensus for methodology for muscle mass and strength assessment. Cachexia is divided into three phases- precachexia to cachexia to refractory cachexia (1).

Multiple agents e.g. appetite stimulants, drugs against cachetic signaling molecules, anti-inflammatory antibodies and anabolic molecules etc have been tried till date to prevent and treat cancer cachexia with no single agent approved so far as gold standard (4). A systemic review published in 2005, identified strong evidence in favor of megesterol acetate and corticosteroids for a short duration as appetite stimulants in cancer patients but their regular use is prevented due to unfavourable safety profile (5). In this review the role of anabolic agents is studied and literature search is done for the same.

OVERVIEW OF ANABOLIC AGENTS

Testosterone or its derivatives are steroid hormones that causes increase in protein synthesis and muscle mass and helps in reducing systemic inflammatory cytokines e.g. TNF-α and IL-6 and it also stimulates the anti-inflammatory cytokine IL-10 (6, 7). They also promotes nitrogen retention and skeletal muscle growth. Although positive effects on body weight, Lean Body Mass (LBM), and functional parameters have been documented in cachexia patients with COPD and HIV/AIDS but studies on cancer patients are limited (8, 9).

Oxandrolone, a modified testosterone derivative with comparatively less androgenic effects, has been approved as an oral anabolic agent for both patients with weight loss during or after surgery, infection etc. catabolic conditions. It is orally administered (approved dosing concentration: 5–20 mg/day) (8). Nandrolone decanoate was approved to stimulate red blood cell production in patients with renal failure, and has been studied in various trials in cachexia patients which are mainly HIV/AIDS and COPD patients and mainly used off label for cancer cachexia patients. It is used with dose ranging from 50mg to 200 mg per week by intramuscular injection (10).

Enobosarm (GTx-024) is an oral nonsteroidal selective androgen receptor modulator (SARM)(11). Although only few studies are available, it has shown tissue-selective anabolic and androgenic activity and can increase muscle mass and function (12, 13).

Side effects of these agents have included elevated transaminase (especially with nandrolone); decreased high-density lipoprotein concentrations and hypogonadism (manifested by decreased systemic testosterone concentrations) and androgenic effects although relatively less with testosterone derivatives. Therapeutic dosages of them rarely lead to serious hepatic adverse effects. They have the potential to cause fluid retention in some individuals (14). However androgenic adverse effects were reported e.g. facial hair growth, acne, alopecia, deepened voice, increased libido but their incidence is very low due to more favorable ratio of anabolic to androgenic potency of the testosterone derivatives. They also interact with oral anticoagulants, oral hypoglycemics, and adrenal steroids thus dose modification is required for these agents.

CLINICAL STUDIES

Case report by Edgar L. Dillon et al although limited to only one cancer patient but have given promising results with testosterone use in maintaining muscle mass during chemotherapy. She was given weekly injection of testosterone enanthate (100 mg intramuscular) along with whey protein.They concluded that concomitant treatment of oral amino acids and testosterone may be a viable therapeutic option for cachexia during chemotherapeutic treatment in terminally ill patient (15).

Another case series in terminally ill patients, one patient was of colon cancer. He was unambulatory due to profound weakness for the first 20 days of admission. Nandrolone 50 mg (intramuscular) was prescribed to assist with weight gain. He gained 4.5 kg following his first dose and was able to ambulate independently. He had already failed dexamethasone and mirtazapine (tried as appetite stimulants). But authors warn that these hormones should be used with caution in critically ill patients. Prior to the intervention they confirmed that there is no evidence of ongoing sepsis (no fevers, increasing inflammatory markers, or broad spectrum antibiotics) or heart disease (no recent myocardial infarction and ejection fraction > 35%); myopathic; receiving sufficient nutrition to make muscle and adequately awake to participate in rehabilitation/physiotherapy (16).

Oxandrolone was given in perioperative setting by Osmolak A M et al in 18 head and neck cancer patients with the aim to improve cancer cachexia. They found statistically significant median differences between the pretreatment and post-treatment prealbumin levels with Oxandrolone administration 10 mg twice daily (BID) for 10 days ($p < .001$)(17).

Nandrolone decanoate 200 mg intramuscularly weekly for 4 weeks was used in non small cell lung cancer patients receiving chemotherapy by Chlebowski R T et al. and they showed a trend for less severe weight loss in the nandrolone decanoate arm versus no additional therapy arm (average weight loss 0.8 ± 0.15 kg *versus* 0.21 ± 0.18 kg, respectively(18).

In a phase II trial by Dobs AS et al, 159 advanced cancer patients with cachexia (≥2% weight loss in the preceding 6 months) were randomized to receive enobosarm 1 mg, enobosarm 3 mg, or placebo for up to 113 days. The primary endpoint was change in Lean body

mass (LBM) from baseline. Significant increase in median LBM was seen in both enobosarm arms, 1 and 3 mg, compared with baseline, 1.5 kg (95% CI, − 2.1–12.6 kg; $P = 0.0012$) and 1.0 kg (95% CI, − 4.8–11.5 kg; $P = 0.046$) respectively, with no improvement in the placebo arm. Quality of life was improved significantly in the enobosarm arms (11).

Another two randomized multicentric trials named as power trials by Crawford J et al have yet to publish their results regarding enobosarm for prevention and treatment of muscle wasting in non small cell lung cancer patients undergoing first line chemotherapy. Probably the results will give further guidance to treat muscle wasting in cachexic patients (19).

CONCLUSION

Recognition of the onset of cancer cachexia, prompt diagnosis and timely intervention are the prerequisites for reduction in morbidity of cancer patients. Although data on anabolic steroids use in cachexia related to other chronic conditions is robust and shown promising results but there is lack of data in cancer patients. A larger cohort is needed to determine the effectiveness of anabolic agents in improving weight gain, quality of life, and survival of cachectic cancer patients. Enobosarm although showing good results but randomized controlled trials are needed to include it as standard approach.

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