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CANCER CHEMOTHERAPY-INDUCED CACHEXIA: THE ORPHAN DISEASE

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ABSTRACT: Cancer remains a major cause of mortality worldwide, with chemotherapy serving as a cornerstone of cancer treatment. While effective in targeting malignant cells, chemotherapy is associated with debilitating side effects, including cachexia a complex, multifactorial syndrome characterized by unintentional weight loss, muscle wasting, fatigue, and reduced physical function. This condition arises from cancer progression and chemotherapy-induced toxicity, compounded by systemic inflammation, oxidative stress, and mitochondrial dysfunction. Chemotherapy agents trigger the release of pro-inflammatory cytokines, promote the generation of reactive oxygen species, and activate the ubiquitin-proteasome system, all of which contribute to skeletal muscle atrophy. The resulting impairment in physical function, diminished treatment tolerance, and worsened prognosis significantly impact patient outcomes. Unlike general cancer-associated muscle wasting, chemotherapy-induced cachexia involves unique mechanisms, including the activation of nuclear factor kappa beta and mitogen-activated protein kinase pathways by agents such as Cisplatin. Cachexia is further aggravated by side effects such as reduced appetite, nausea, and fatigue, leading to myosteatosis and deterioration in muscle mass and function. Current therapeutic approaches include pharmacological agents such as ghrelin receptor agonists, selective androgen receptor modulators, omega-3 fatty acids, nutritional support, and physical exercise. However, these interventions remain inadequate. Given the central role of mitochondrial dysfunction in muscle wasting, mitoprotective compounds hold promise as targeted therapies. A comprehensive approach integrating pharmacological, nutritional, and exercise-based strategies is essential for effective management. Despite the absence of approved treatments, ongoing research aims to develop novel therapies to preserve muscle mass and enhance the quality of life for cancer patients.

INTRODUCTION:

Cancer and Chemotherapy: Cancer is a significant global health issue and ranks as the second leading cause of death in the United States. Cancer is characterised as the proliferation of abnormal cells without regulation in any part of the body.

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It is well acknowledged that cancer can arise when the regular physiological processes of the body cease to function. Old cells undergo uncontrolled growth, giving rise to new abnormal cells, instead of undergoing programmed cell death. Tumour [1] is a mass of tissue that can be formed by these additional cells.

World Health Organisation states that cancer can develop as a result of the interplay between an individual's genetic elements and three types of external agents: physical carcinogens (such as ultraviolet and ionising radiations), chemical carcinogens (for example asbestos, arsenic, tobacco smoke chemicals, and aflatoxin), and biological

carcinogens (infections caused by bacteria such as Helicobacter pylori; which is linked to development of gastric adenocarcinoma, viruses such as Human Papillomavirus; which is strongly associated with cervical cancer; and Epstein-Barr Virus which is associated with several types of cancers, including Burkitt lymphoma, Hodgkins lymphoma, or parasites such as Schistosoma haematobium which is linked to bladder cancer [2]. Cancer patients receive treatment based on the specific type and stage of their cancer. Traditional therapies, including surgery, radiotherapy and chemotherapy are often used. Alternatively, newer treatment modalities such as hormone therapy, immunotherapy, targeted therapy, photodynamic therapy and gene therapy are employed [3].

Radiotherapy employs use of high levels of radiation to reduce or eliminate cancer cells. However, chemotherapy is a widely used and effective modality of treating cancer, involving the administration of one or more chemotherapeutic drugs or alkylating agents. The term "chemotherapy" refers to a class of anti-neoplastic drugs identified in the 18th century, and were used as either the primary or supplemental treatment for almost all forms of cancer. Chemotherapy primarily focuses on inducing cell cycle arrest *via* pathways leading to DNA damage, which ultimately leads to apoptotic cell death. However, these drugs are categorised into several categories based on their specific mechanism of action. Regardless of their distinct mechanisms, chemotherapies continue to be successful in causing cancer cell death to reduce the overactive growth of neoplastic cells. Although chemotherapy demonstrates anti-cancer effectiveness, it additionally causes side effects to normal cells because of their non-cell-specific toxicity.

Systemic toxicity is prevalent among the haematological system. Chemotherapy drugs often target rapidly dividing cells, such as cells in the bone marrow, often leading to anaemia, leukopenia, and thrombocytopenia. The peripheral and central nervous system also get affected with the use of drugs such as vincristine and paclitaxel, which can cause symptoms of peripheral neuropathy. Cognitive changes such as impaired memory and difficulty in concentration, with confused behaviour, are also not uncommon with use of chemotherapeutic drugs. Examples include Cisplatin, which is documented to cause neurotoxicity and Doxorubicin, Paclitaxel which are linked to cognitive deficit in some patients. The cardiovascular system also gets impaired with doxorubicin which can cause damage to heart muscles, often leading to cardiomyopathy and heart failure, commonly referred to as anthracycline-induced cardiotoxicity. Among the integumentary system, alopecia is also very common with use of many chemotherapeutic drugs along with dermatological manifestations such as skin dryness, rashes and photosensitivity.

Among the gastrointestinal system, nausea, vomiting and mucositis are also commonly seen. Several chemotherapeutic drugs arrest the process of cell cycle as their principal mechanism of action for combating the rapid proliferation of cancer cells. This leads to noticeable adverse effects in cells that have a high turnover rate, such as cells in skin, hair, gastrointestinal epithelium and bone marrow. New research shows that there is also impact on myosatellite (stem) cells which normally divide and multiply quickly when muscles are damaged (like when there is muscle inflammation) or when growth factors (like androgens and growth hormones) are present. This contributes to the overall reduction in observed muscle mass during cachexia [4]. In recent years, there has been growing interest in understanding the non-specific effects of chemotherapy-induced toxicity on the skeletal muscle system [5, 6]. More precisely, chemotherapeutic drugs cause a decrease in body mass together with atropy and an impairment of skeletal muscle function, which is known as cachectic myopathy.

The adverse effects become apparent when patients in the oncological context experience deconditioning. Fatigue and Weight loss are two significant disabling phenomena that are particularly prevalent in metabolic wasting syndrome, known as cachexia [7]. Over the past sixty years, there has been a significant increase in the research and development of many more effective anticancer drugs. Alongside a more logical approach to using radiation and surgery, this has improved the effectiveness of treating various kinds of cancers. It has also given a genuine opportunity of prolonging remission to patients diagnosed with

cancer, enhancing their quality of life, and increase their likelihood of survival. In certain instances, patients have even been cured of the disease. Chemotherapeutic drugs exert their effects through several mechanisms, which are likely to impact the extent to which they might cause cachectic myopathy. Nevertheless, among the drugs that cause myopathy, there are certain shared fundamental mechanisms [6].

One school of thought proposes that chemotherapy might induce systemic inflammation *via* having an effect on the central nervous system. More specifically, it can stimulate the hypothalamus-pituitary adrenal (HPA) axis, which triggers an adaptive illness response. The release of glucocorticoids and the generation of pro-inflammatory cytokines, for example IL-1, IL-6 and TNF- α are both induced concurrently by this response and are important factors in the development of skeletal muscle atrophy. The specific cause of skeletal muscle atrophy can be directly attributed to an excessive generation of pro-inflammatory cytokines by engaging membrane receptors and activating a transcription programme that promotes muscle breakdown [6, 7].

Initiation of the inflammatory microenvironment triggered by chemotherapy enhances gene expression REDD1 (Regulated in development and DNA damage response 1) linked to skeletal muscle atrophy. The transcription of REDD1 controls the adaptive stress response, which involves activating stress-sensitive molecular targets such as nuclear factor-kappa light-chain enhancer of activated B cells (NF-B) and mitogen-activated protein kinase (MAPK) [8, 9]. During oxidative stress, these two targets have similar signaling cascades. Specifically, the activity of MAPK stimulates the process of phosphorylation of the NF-B component, p65, leading to the activation of NF-B and initiation of skeletal muscle atrophy. The atrophic response is predominantly accomplished by the transcription of MuRF-1, classic atrogenes, Atrogin-1 and the E3 ubiquitin ligases by means of ubiquitin-proteasome system (UPS) [10]. In addition, studies have shown that various chemotherapeutic drugs may promote the generation of reactive oxygen species (ROS) in C2C12 myotubes, leading to improper myotube morphometry [11, 12]. These findings indicate that stress-sensitive molecular targets may serve as shared signaling mechanism in chemotherapy-induced cachexia. Moreover, a disproportionate generation of reactive oxygen species (ROS) is linked to the initiation of mitochondrial dysfunction, which is hypothesised to be the key factor in the development of chemotherapy induced skeletal muscle wasting [13]. Myoprogenitor activity (Satellite cell replication) is impacted by chemotherapy agents, in addition to fact that these drugs selectively target differentiated skeletal muscle tissue. This has significant implications for skeletal muscle turnover, repair and growth [14].

Cachexia: Cachexia is a term derived from the Greek words "kakos" and "hexis," which respectively indicate "bad" and "condition." The cachectic state is commonly encountered in several clinical diseases, including cancer, chronic heart failure, chronic obstructive pulmonary disease (COPD), and sepsis. Developing a standardised definition of cachexia has been deemed crucial in the present world. In December 2006, a panel of global specialists convened in Washington DC (USA) for an international consensus meeting arranged by the Society for Cachexia and Wasting Disorders.

During this Meeting, the Experts Made the Following Statement: "Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with wasting disease. Wasting disease is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity [15]." Cachexia defined by European Palliative Care Research Collaborative Organization is a multifactorial syndrome with "a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism [16]." A key defining feature is ongoing loss of skeletal muscle mass which cannot be fully reversed by conventional nutritional support, leading to progressive functional

impairment [16]. Cachexia is a wasting condition caused by excessive catabolism in both skeletal muscle and adipose tissue. It greatly complicates patient care, decreases tolerance for and the efficacy of anti-cancer treatment, and is responsible for mortality in up to 30% cancer patients [7]. Cachexia is characterised by a substantial decrease of body mass brought on by muscular atrophy. More than half of cancer patients suffer from this devitalising condition, that is cachexia [17]. Quality of life and survival are negatively impacted by cachexia, yet there are currently no viable treatments. To date, most anti-cachexia efforts have concentrated on preserving skeletal muscle mass, so that patients can continue to be in good physical condition during their cancer treatment [18].

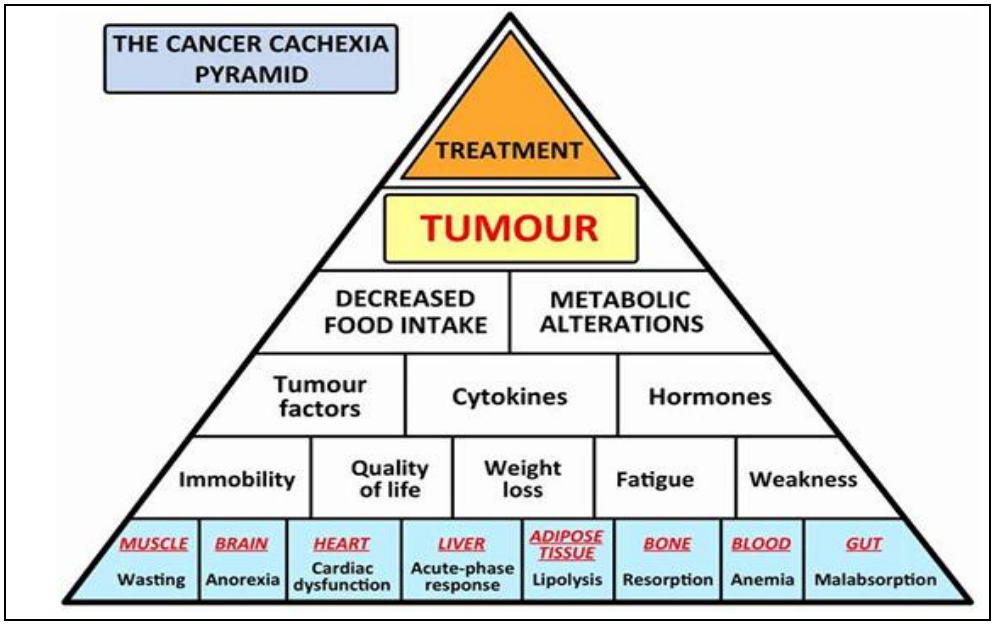

FIG. 1: CANCER CACHEXIA PYRAMID ILLUSTRATING THE CONDITION AS A MULTI-ORGAN SYNDROME [19]

Fig. 1 illustates the cancer cachexia pyramid which incorporates several key variables contributing to this syndrome. Cachexia not only impacts skeletal muscle, but also affects several other organs including the bone, heart, liver, adipose tissues and brain. Cachexia is a complex disorder marked by a steady body mass loss and composition, particularly lean mass, and may also involve the loss of fat mass.

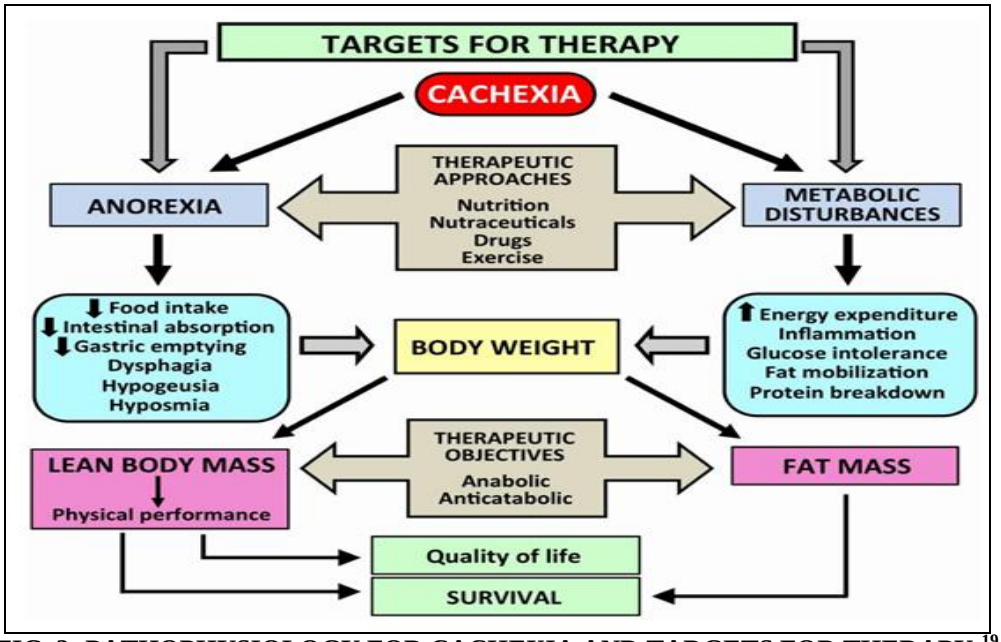

FIG. 2: PATHOPHYSIOLOGY FOR CACHEXIA AND TARGETS FOR THERAPY [19]

It is usually accompanied by a gradual decline in physical function. Skeletal muscles are the primarily affected organ in cachexia, and this is caused by numerous factors such as systemic inflammation, metabolic dysregulation, insulin resistance, and anorexia [20]. Skeletal muscle mass plays a crucial role as a prognostic sign in diagnosing cachexia. This is due to the fact that an increase in adiposity reduces the effectiveness of using body weight and body mass index (a basic measure of body composition) for diagnosing cachexia [21]. Cachectic myopathy, once initiated, creates a vicious cycle with a higher chance of toxicities connected to dosage, affecting the clinical decision making process and patient risk assessment. Treatment effectiveness is hampered as a result, raising morbidity as well as mortality risk through dose reduction or treatment discontinuation [22].

Cachectic myopathy occurs as a consequence of two insults in conjunction with one another: (1) interactions between cancer and the host, and (2) Chemotherapeutic cytotoxicity [20, 23]. Although they are generally lifelong, their effects can also be acute. The amount of research on cachexia is growing at an exponential rate, but the number of studies that concentrate on the impact of chemotherapy is significantly smaller [6]. Cachexia is a substantial challenge for both patients and healthcare professionals. It is estimated that cachexia impacts 50-80% of cancer patients and contributes to 20% of cancer related fatalities [24]. Currently, there are no other therapeutic options available for body mass loss other than typical dietary therapies, which have proven to be generally ineffective [19].

Chemotherapy is a life-saving modality of treatment for cancer patients. It affects whole body causing harm, especially to the rapidly growing cancer cells as well as healthy cells. An injury to healthy cells leads to adverse effects such as weight loss, fatigue, weakness of muscles, nausea, and vomiting. Chemotherapy may lead to rapid generation of mitochondrial reactive oxygen species (mtROS) and dysfunction resulting in loss of muscle, impairment of regenerative capacity, pain, fatigue, and exercise intolerance. The leading cause of suffering due to cachexia in cancer patients is attributed to oxidative stress mediated by ROS [14]. The main factor causing cachexia is tumour growth. Chemotherapy is a significant contributor to cachexia's aetiology [25]. Chemotherapy also has the potential to cause oxidative stress, inflammation, ubiquitin-dependent catabolism and nitrogen imbalance [12]. The advancement of cachexia may be more enhanced by these negative reactions than by the tumour itself [26]. Thus, in addition to cancer-induced cachexia, chemotherapy-induced cachexia exacerbates the condition, leading to profound loss of muscle mass and function. Damage to mitochondria from combination chemotherapy may also reduce oxidative phosphorylation-related proteins like Cytochrome-C and PGC-1α (Protein transcription coactivator peroxisome proliferator-activated receptor gamma coactivator 1-alpha), which governs energy metabolism, generation of mitochondria, and metabolism of muscle fibres.

Muscle oxidative stress and an increase in ROS production have both been linked to chemotherapy. Chemotherapy raises levels of tumour growth factor beta (TGF-β), this in turn upregulates myostatin and shifts the metabolic balance away from anabolism and toward catabolism. Microvasculature in muscles can be diminished by chemotherapy's anti angiogenesis effect [27].

Difference between Cancer-Induced Cachexia and Cancer Chemotherapy-Induced Cachexia: Recent studies have suggested that loss of muscle due to cancer differs from cancer chemotherapy-induced muscle loss despite having some similarities [29]. Muscle fibres are vulnerable to adverse effects of cancer chemotherapy since they are dependent on cellular turnover and contain dense nuclei. Cisplatin restricts the growth of tumor but may produce wasting of skeletal muscles as well as adipose tissues, commonly referred to as cancer chemotherapy-induced cachexia [30]. Daumrauer *et al.* demonstrated that chemotherapy can promote cancer chemotherapy induced cachexia by activating a muscle atrophy process. They examined the effect of Cisplatin, a standard chemotherapeutic agent, on a colon-26 murine cancer cachexia model and reported that although Cisplatin is able to strongly reduce tumour burden, it can also promote muscle atrophy through activation of nuclear factor κB (NF-κβ) pathway [31]. Most research on cancer chemotherapy-induced

cachexia are observational / retrospective in nature, and therefore lack a comparator arm of patients who did not undergo chemotherapy. Muscle mass loss following oncology treatment may, in theory, be caused in part by the tumor's unrestrained protein catabolism. Patients with more aggressive tumours, such as pancreatic cancer, have the most marked reduction in fat-free mass over time in comparison to those with other primary cancers. Adverse effects during chemotherapy, such as exhaustion, lack of appetite, nausea, vomitting, and diarrhoea, have been noted by some experts to have a significant impact on a patient's ability to eat, stay active, and prevent the rapid atrophy of muscle tissue [32].

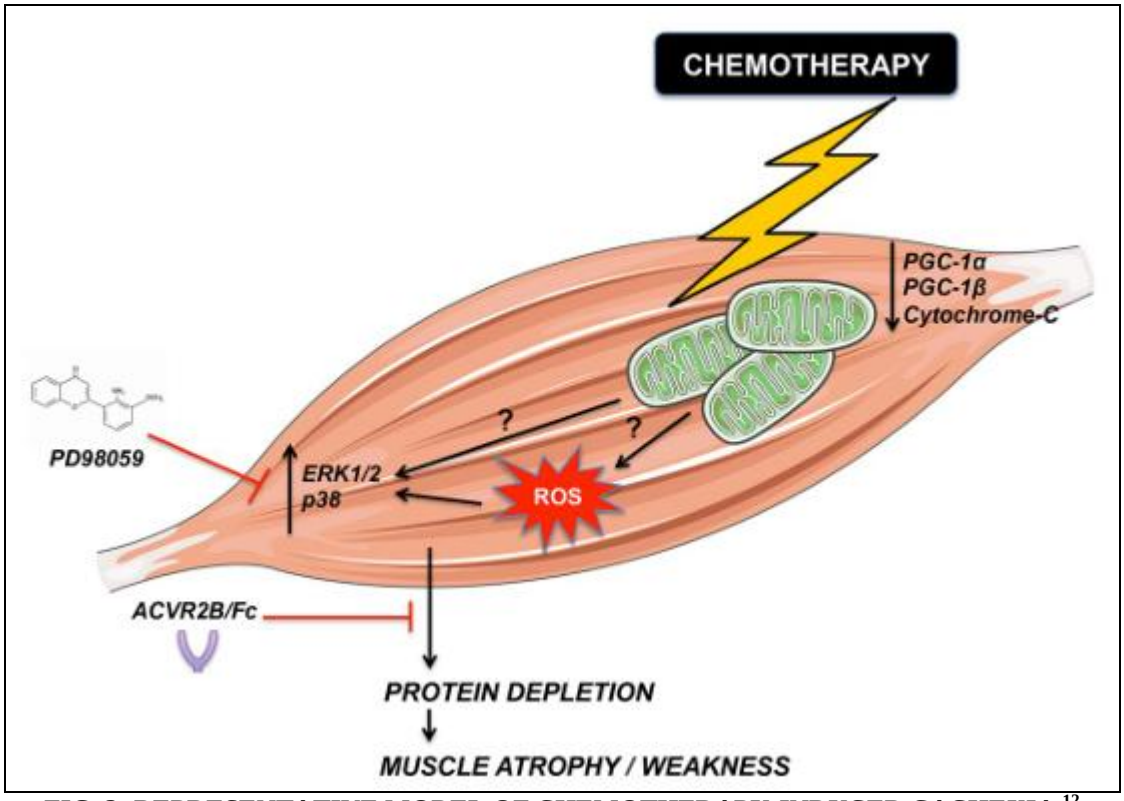

FIG. 3: REPRESENTATIVE MODEL OF CHEMOTHERAPY-INDUCED CACHEXIA [12]

Fig. 3 shows a Chemotherapy results in depletion of mitochondria and ERK1/2, MAPKs dependent pathways activation, in direct or indirect ways. All of these changes might result in cachexia. Muscle wasting can be avoided by either inhibiting ERK1/2 activation with MEK1 pharmacologic inhibitor PD98059. Muscle growth can also be promoted by taking advantage of ACVR2B/Fc. ACVR2B/Fc (Soluble Activin Receptor 2B) is a widely studied myostatin inhibitor, and PD98059 is a MEK1 pharmacologic antagonist [12] **Fig. 5.** Studies to date demonstrates a clear relationship between chemotherapy and muscle metabolism. In actuality, chemotherapy that is given post-operatively to ostensibly tumour-free patients, also causes skeletal muscle wasting [28]. Pin *et al.* recently conducted an experiment in which they compared CD2F1 male mice divided into 4 sets: those given vehicle treatment (V), those given C26 tumour hosts (CC), those given Folfiri treatment (F), and those given C26 tumour hosts plus Folfiri (CC+F, CCF) [29]. There was a statistically significant decrease in skeletal muscle mass between the experimental arm and the control arm; the CCF combination led to the greatest decrease in quadriceps mass. 5-flurouracil, leucovorin, and irinotecan were found to work together through activating 'mitogen-activated p38 protein kinase' and 'ERK1/2' pathways, but not the ubiquitin proteasome pathway (UPP) [12]. The first hypothesis connecting an increase in muscle mass to disease stability was offered by Prado *et al.* During the course of cancer illness, these investigators discovered that 15% of patients with advanced cancer acquired muscle mass, while roughly 50% stayed steady. Patients who saw substantial increases in muscle mass responded well to therapy, maintained an adequate nutritional status,

and had manageable symptom severity, whereas those who experienced substantial decreases in muscle mass suffered fast illness progression and poor prognosis [33]. Daly *et al.* concluded that patients who demonstrated a good response to neoadjuvant chemotherapy with lesser tumour burden experienced decreased muscle loss [34]. Similar findings were also reported in lung and gastric cancer patients; and by Miyamoto *et al.* regarding progression-free survival [35]. However, Selumetinib (a kinase inhibitor anti-cancer drug) helped in gaining weight and muscle mass in nearly 80% of biliary cancer patients treated with it, whereas only 12% of the patients had an objective response to it, indicating that the anabolic effects of a drug are separate from its anti-cancer action [36].

Dijesterkhuis *et al.*, and Paireder *et al.* discovered no link between alteration in muscle mass and progression-free survival, and Parsons *et al.* asserted that sarcopenia was evident in 1/3rd of patients with reduced tumour size after treatment, and in more than half patients with enlarged tumour size [37, 38]. Infiltration of Adipose tissues inside the muscles is reflected by skeletal muscle attenuation, which lowers the "quality" of skeletal muscles. In addition to being a significant predictor of clinical outcomes for cancer patients and occasionally a superior predictor of prognosis than muscle mass alone, muscle attenuation, also known as "myosteatosis," serves as a more realistic representation of muscle function. Since an increase in adipose tissue infiltration appears to begin prior to the depletion of muscle mass, sarcopenia would follow a course of slower muscular attenuation [39]. Clinical studies have demonstrated that taking n-3 fatty acid supplements can reduce muscle loss and myosteatosis. This is because insufficient serum levels of EPA (Eicosapentaenoic Acid) and DHA (Docosahexaenoic Acid) commonly occur along with muscle mass loss and myosteatosis. But the mechanism is still not clear, and it seems that adipogenic genes are expressed more in skeletal muscle in people with cancer. CCAAT/enhancer-binding protein beta (C/EBPβ) is a powerful activator of adipocyte proliferation and differentiation.

C/EBPβ, δ, and α as well as peroxisome proliferator-activated receptor gamma (PPARγ), are transcription factors that play a role in the expression of adipocyte genes. Adipose tissue's decreased buffering capacity of fatty acids in circulation as a result of chronic inflammation may lead to elevated levels of ceramides and diacylglycerol in skeletal muscles. Cancer-related insulin resistance may reduce lipid-storing ability by reducing the inhibition of lipolysis. This may increase blood levels of non-esterified fatty acids (NEFA), which may be deposited in ectopic locations such as the liver and muscles [40].

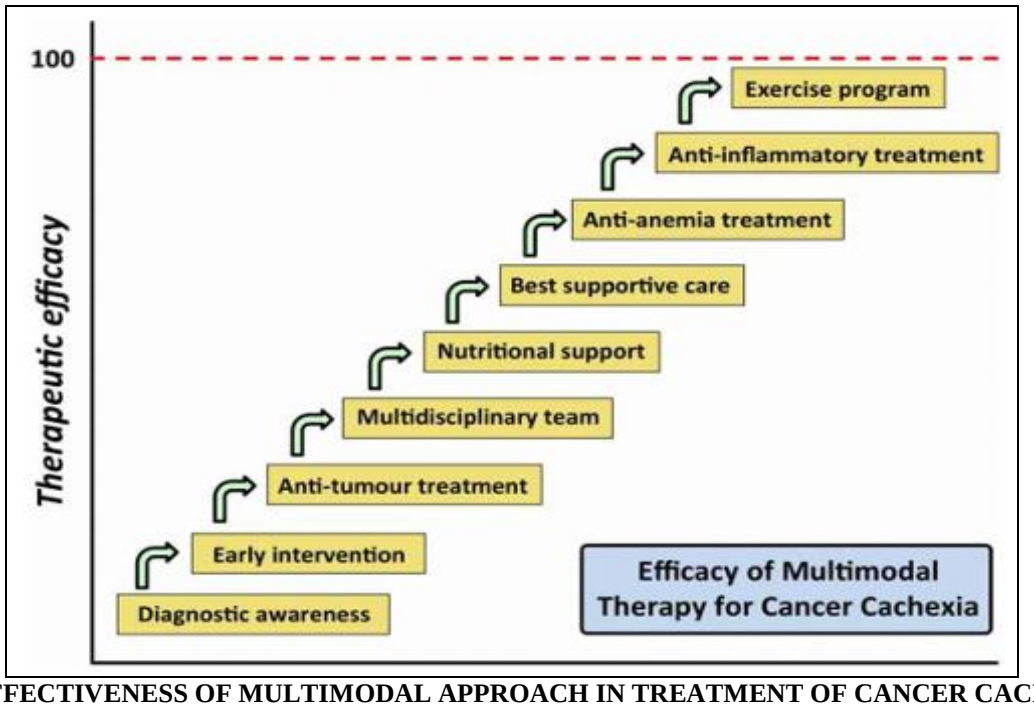

FIG. 4: EFFECTIVENESS OF MULTIMODAL APPROACH IN TREATMENT OF CANCER CACHEXIA [19]

Fig. 4 Illustrates the effectiveness of multimodal approach in treatment of cancer cachexia. It is improbable that a single medication could reverse the cachectic process. Only by sequentially applying multiple treatment interventions/ approaches we can hope to achieve 100% efficacy in the treatment of cachexia in nearby future [19].

At present, cachexia is a notable problem in cancer that has not yet been well addressed, as there is no approved medication available for clinical use. The intricacy of this syndrome, particularly at the skeletal muscle level, is the most probable cause. Several variables contribute to the development of myopathy during anti-cancer treatment. For instance, the weakening of muscles caused by variables related to hospitalisation, such as lengthy periods of being confined to bed rest, limited chances to engage in physical exercise, and feelings of depression or exhaustion, might have a significant role in the advancement of cachexia during chemotherapy treatment Several ongoing research are being conducted to develop treatment options for alleviating the debilitating symptoms of cachexia. These investigations involve numerous candidates that have demonstrated promising results. These therapies encompass physical exercise and the use of pharmaceutical or nutraceutical adjuvants [41]. Mitochondrial dysfunction is a crucial molecular event that leads to the development of cachectic myopathy [42]. More precisely, the deterioration of mitochondria is proposed as a precursor to muscle wasting in cachexia [43] making it a crucial focus for early intervention in treatment.

Current Treatments Available: There are several methods available to increase or preserve muscle mass while undergoing chemotherapy. The following are discussed only those treatments (medications, nutritional supplements or physical activity) that have been proven effective in oncology patients undergoing chemotherapy via randomized clinical studies.

Ghrelin: An endogenous GHSR-1a (growth hormone secretagogue receptor - 1a) ligand, ghrelin has been found to prevent muscle atrophy by downregulating inflammation, p38/C/EBP /myostatin, and activating myoD, Akt and myogenin. This protective effect is shown even when Cisplatin is administered. Daily oral administration of 100 mg of the active, high-affinity, selective ghrelin-receptor agonist, Anamorelin for 12 weeks resulted in an increase in lean body mass, according to results from two randomized controlled trials [44, 45]. With 50 mg of Anamorelin similar effects were witnessed [46].

Enobosarm: Enobosarm is a selective non-steroidal androgen receptor modulator tissue-specific anabolic drug. Total lean body mass significantly increased by day 113 when compared to baseline values and control group after treatment with Enobosarm at a once-daily oral dose of 1 mg or 3 mg for 4 months. And as compared to a placebo, testosterone 100 mg weekly for 7 weeks resulted in greater gains in lean body mass with no negative side effects.

Omega-3 Fatty Acids: The use of omega-3 fatty acid in sarcopenia/myosteatosis is supported by two distinct lines of thought. Reducing the n-6/n-3 ratio in a preclinical model of colon cancer lowered the expression of PPARγ and prevented adipogenesis in 3T3-L1 pre-adipocyte cell line. Adipocyte gene expression is regulated by a number of transcription factors, including (C/EBP)β, δ, α and peroxisome proliferator-activated receptor (PPARγ) (Al Saedi *et al.,* 2022). Recent experimental research by Almasud *et al.* found that both long-term and fish-oil supplements proved equivalently beneficial in reducing chemotherapy-associated myosteatosis (from irinotecan + 5-fluorouracil) and improving tumour responses to chemotherapy [47].

Three randomized controlled trials found that a daily dose of 1.5- >5.1 g of EPA for 1-2 months was effective in preserving or enhancing fat-free mass whereas another found no such effect [48].

Oral Supplementation and Enteral Nutrition: Patients undergoing first-line chemotherapy for metastatic colorectal cancer were studied in a randomized controlled trial (RCT) that examined the impact of nutritional counselling (high protein diet + some sort of physical activity) on the rate of change in muscle mass. Muscle mass was not affected by the therapy, according to the study. It is worth noting that there exists statistically significant link between protein consumption and

change in muscle mass, although this may have been attributable to contamination of control group, which also got a high-protein intake. In comparison to a control group, the authors discovered that those who received dietary guidance had a greater chance of gaining weight. In comparison to a control group, the authors discovered that those who received dietary guidance had a greater chance of gaining weight and a longer progression-free and overall survival [48]. High-fat diets may help preserve cell mass in the body [49].

Parenteral Nutrition: Obling *et al.* conducted a randomized controlled trial50 of a strategy comprising of adjuvant Parenteral nutrition + nutritional guidance; they aimed to provide 30 KCal / kg / day and protein 1.5 gm / kg /day (25-35% of RDA) for period of 24 weeks, and they found that the parenteral nutrition arm had a statistically significant improvement in fat-free mass at week 12, but there was no difference at weeks 6, 18, or 24.

Exercise: Patients undergoing treatment for gastrointestinal cancer demonstrated an increase in lean body mass as measured by bioelectrical impedance measurement after participating in a home-based physical activity programme consisting of 150 minutes of moderate walking per week [51].

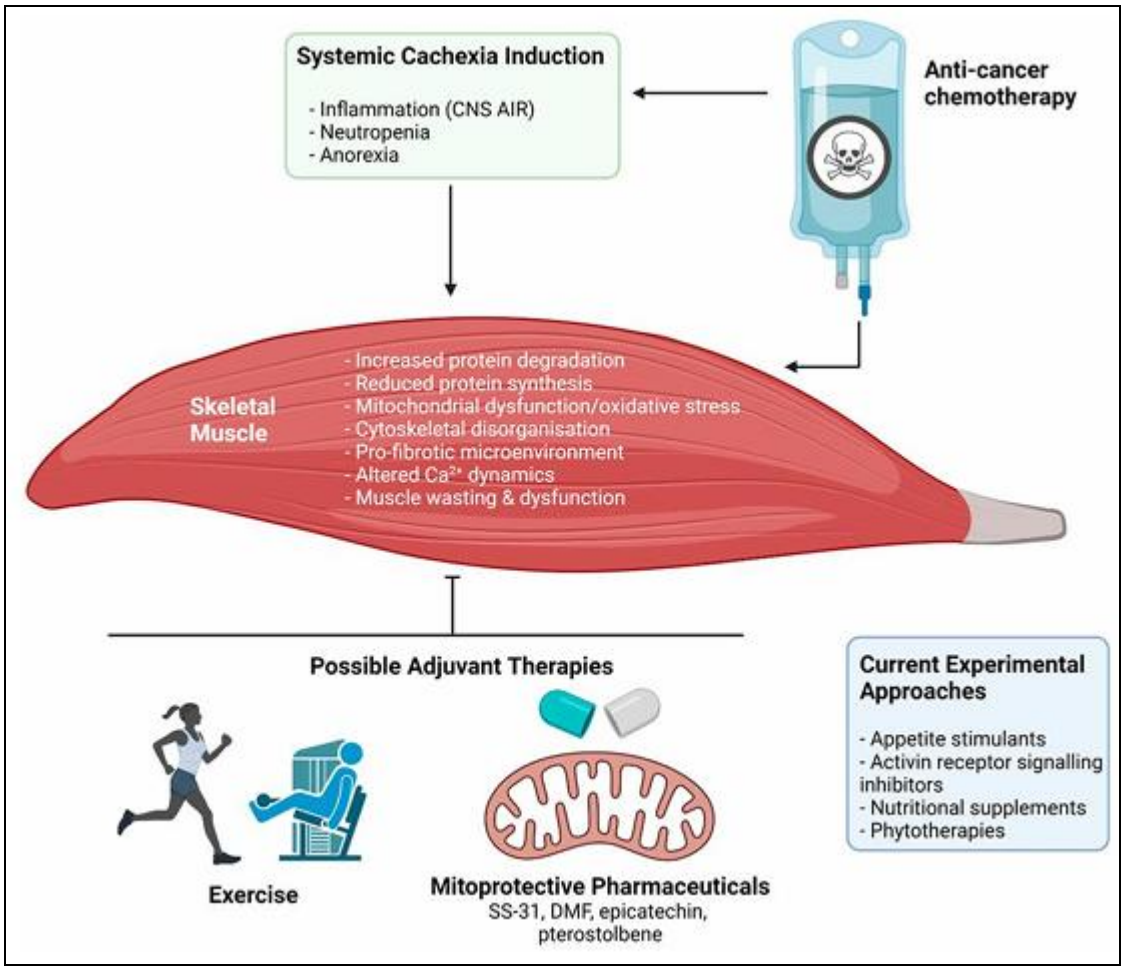

FIG. 5: INFLUENCE OF CANCER-CHEMOTHERAPY TREATMENT ON CACHECTIC MYOPATHY AND POTENTIAL PREVENTIVE THERAPEUTIC MEASURES [52]

Fig. 5 highlights the influence of cancer-chemotherapy treatment on cachectic myopathy and potential preventive therapeutic measures. In clinical cancer treatment, chemotherapeutic drugs can affect skeletal muscle through the initiation or augmentation of systemic cachexia, both in direct and indirect ways. The outcome is the commencement of a programme which promotes skeletal muscle wasting and dysfunction. This programme includes: enhanced breakdown of muscle proteins, a decline in the protein bio-synthesis, impaired functioning of mitochondria

and increased oxidative stress, irregularities in the cytoskeleton organisation and decrease in levels of crucial cytoskeletal proteins which stabilize the muscle membrane, activation of signalling pathways that promote fibrosis in the extracellular matrix, and an alteration in the calcium (Ca2+) dynamics. The consequence is wasting of muscle tissue and impaired function, resulting in weakness and fatigue among patients. This condition restricts their ability to do everyday tasks and worsens their overall quality of life. Various treatment strategies are presently under investigation to safeguard against or address these symptoms, such as appetite stimulants, inhibitors of activin receptor signalling, phytotherapies and nutritional supplements. Novel therapeutic approaches may involve the implementation of physical activity and the use of mitoprotective compounds such as dimethyl fumarate (DMF), SS-31, Pterostilbene, BGP-15, and epicatechin.

CONCLUSION: Cancer chemotherapy-induced cachexia is a multifaceted syndrome with significant impacts on muscle metabolism, leading to muscle atrophy, weakness, and reduced quality of life. Various mechanisms, including mitochondrial dysfunction, inflammation, and altered protein synthesis, contribute to muscle wasting. While no approved treatment exists, emerging therapies, including pharmacologic agents, nutritional interventions, and exercise, show promise in mitigating muscle loss. A multimodal approach integrating these strategies may offer the most effective means to manage cachexia and improve patient outcomes during chemotherapy.

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