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Review Article

Anorexia–cachexia syndrome in pancreatic cancer: Recent advances and new pharmacological approach

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ABSTRACT

About 80% of all pancreatic ductal adenocarcinoma patients suffer from a wasting syndrome referred to as the "cancer anorexia–cachexia syndrome" (CACS) characterized by abnormally low weight, weakness and loss of skeletal muscle mass with or without loss of body fat, which directly impacts overall survival, quality of life, and physical activity. The aim of this review was to examine recent findings about CACS' pathophysiology and to describe the current pharmacological approaches. In recent years many efforts were made to improve our knowledge of CACS; currently we know that cachexia arises from a complex and multifactorial interaction between various mechanisms including inflammation, anorexia/malnutrition, alterations of protein and lipid metabolism; consequently its management requires multidisciplinary and multipharmacological approach that should address the different causes underlying this clinical event. On these premises, several drugs have been proposed starting from the first pharmacological treatment based on progestational agents or corticosteroids; most of them are in the preclinical phase, but some have already reached the clinical experimentation stage. In conclusion, to date, there is no standard effective treatment and further studies are needed to unravel the basic mechanisms underlying CACS and to develop newer therapeutic strategies with the hope to improve the quality of life of pancreatic cancer patients.

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1. Introduction

Pancreatic ductal adenocarcinoma (PDA) is currently one of the most aggressive gastrointestinal carcinomas accounting for a 5-year survival rate of less than 5% and a death-to-incidence ratio of 0.99 [1].

Despite important treatment progress, the survival rate of patients with PDA has not significantly improved over the last few decades [2]. Close to 90% of PDA have advanced disease at presentation; as a consequence, palliative care is the only treatment option for most of these patients. On the other hand, even when the neoplasm is suitable for resection, surgery offers a five-year survival rate of about 25% [3]. Almost all patients with PDA develop metastases and die from the debilitating metabolic effects of their unrestrained growth. The median survival of patients with locally advanced and metastatic disease is 6–9 months and 3–6 months, respectively [4,5]. One reason contributing to this high

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mortality is cancer cachexia, defined as an unintended weight loss of more than 10% in 6 months, which is present in more than 80% of PDA [6,7], with progressive body fat and muscle tissue wasting with associated worsening of their clinical status, lower quality of life and a high mortality rate.

Over the last few years, important new developments regarding the pathogenesis of pancreatic cancer cachexia have been achieved in order to identify palliative measures in this patient population that could also be cost effective [8]. Knowledge of the mechanisms of cancer anorexia–cachexia syndrome is of great importance to lead to effective therapeutic interventions for several aspects of the syndrome. Nevertheless, cachexia remains a poorly understood process whose mechanisms have received only limited attention from cancer researchers [9]. More clinical research is needed to clarify this important subject [10].

2. Review

2.1. Definition and pathogenesis of anorexia–cachexia in pancreatic cancer

Many patients with advanced cancer undergo a wasting syndrome characterized by anorexia, loss of weight, asthenia, and a poor prognosis, referred to as the "cancer anorexia–cachexia syndrome" (CACS) [11].

In cancer patients, anorexia and cachexia can co-exist; while anorexia is defined as the loss of the desire to eat, which frequently leads to reduced food intake, cachexia is characterized by profound loss (up to 80%) of both adipose tissue and skeletal muscle mass that eventually leads to hypoalbuminemia and asthenia, which, together with anemia, a frequent comorbidity in cancer patients, limit physical activity and consequently inhibit protein synthesis [12]. Loss of both skeletal muscle and fat distinguishes it from starvation (where lean body mass is preserved at first).

CACS impacts not only upon prognosis but also on patients' quality of life [13]; actually cachexia is so destructive that this process taps into other sources of energy, namely skeletal muscle and adipose tissue when energy expenditure exceeds food intake. As a consequence, nutritional status is compromised in direct response to tumor-induced alterations in the metabolism [14]. Moreover cachexia adversely affects the immune response of the host against infections and withstand treatment by chemotherapy and radiotherapy. Weight loss is an important prognostic factor in cancer; the higher the extent of weight loss, the shorter the survival time [15]. Reduction in food intake (<1500 kcal/day), together with a weight loss of 10% or greater and a systemic inflammatory response are considered prognostic parameters. Weight loss and the wasting process cannot be reversed by nutritional supplements in cancer patients. Patients with CACS die when there is 25–30% of total body weight loss, but weight loss alone cannot be a prognostic factor, because it cannot identify the complete effect of cachexia. Proteolysis-inducing factors which cause wasting, and increased energy expenditure have been identified, and they are also considered as important factors that contribute to the wasting process [16,17].

Unfortunately, there is no clear consensus definition of this common problem in cancer patients leading to an insufficient knowledge of the etiology of the condition. Earlier definitions of cachexia stated "a wasting syndrome involving loss of muscle and fat directly caused by tumor factors, or indirectly caused by an aberrant host response to tumor presence" [18]. However, more recent definitions have downplayed the importance of fat loss and describe cachexia as "a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass" [19], thus highlighting the unique consequences of muscle wasting—the hallmark of cachexia. A recent consensus definition has been proposed to include further factors to diagnose the cachexia syndrome such as involuntary weight loss, decreased muscle mass, anorexia, and biochemical alterations (C-Reactive Protein (CRP), albumin, hemoglobin [16,19]).

CACS arises from a complex interaction between cancer growth and host response resulting in progressive weight loss that is the consequence of a negative protein and energy balance often associated with signs of inflammation [20]. The mechanism by which PDA provokes the loss of the host's muscle mass is presently thought to be complex and multifactorial. It involves multiple pathways: procachectic and proinflammatory signals from tumor cells, systemic inflammation in the host, and widespread metabolic changes (increased resting energy expenditure and alterations in metabolism of protein, fat, and carbohydrate). Whether it is primarily driven by the tumor or as a result of the host response to the tumor has yet to be fully elucidated [21]. The pathogenesis of CACS in PDA is summarized in Fig. 1 [10]; in synthesis, PDA can lead to a reduction in nutritional intake, because of pancreatic cancer-associated stenosis of the duodenum or maldigestion with exocrine pancreatic insufficiency, malaise, taste alterations and/or loss of appetite. In addition, early satiety due to a lack of gastric accommodation, gastroparesis or delayed pyloric emptying is always present and it is accompanied by early postprandial bloating and severe nausea [10]. This condition may be worsened by the side effects of treatment such as radiotherapy or chemotherapy which decrease food intake. It is also a common experience for physicians to observe deep changes in smell and taste in PDA, with frequent aversion to specific foods capable of recalling unpleasant feelings, thus contributing to increasing anorexia [10].

Although anorexia is a common symptom in cachexia, it should not be used as a synonym. Cachexia is associated with characteristic metabolic alterations that are not present in anorexia [22]. While loss of appetite and resultant decrease in energy intake undoubtedly contribute to weight loss associated with cancer cachexia, whether anorexia occurs by an independent process or is a result of the inflammatory process of cachexia is not

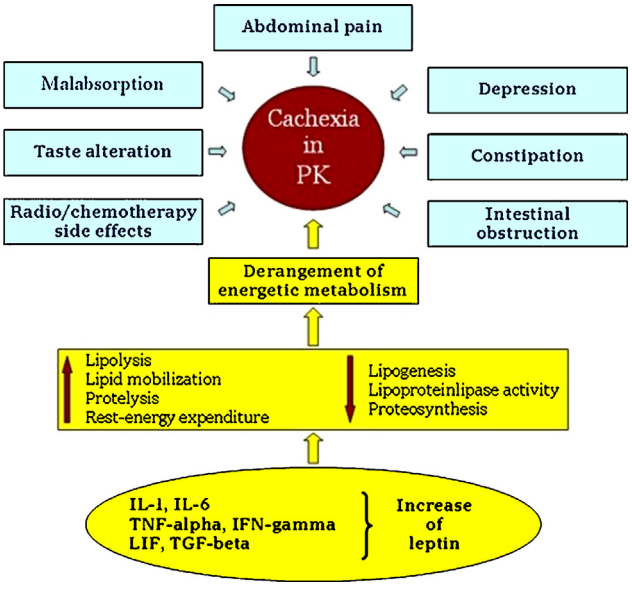

Fig. 1. Pathogenesis of cachexia in pancreatic cancer (PK: pancreatic cancer; IL-1: interleukin-1; IL-6: interleukin-6; TNF-alpha: tumor necrosis factor-alpha; IFN-gamma: interferon-gamma; LIF: leukemia inhibitor factor; TGF-beta: transforming growth factor-beta).
Modified from: Uomo et al. [10].