

Searching for the Ideal Therapy for Cancer Cachexia

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Editorial

Although megestrol acetate and corticosteroids have been, and still are, the universal drug approaches for the treatment of the cancer cachectic syndrome, novel drugs and treatments have led to promising approaches to counteract wasting thus improving the quality of life and, possibly, survival of cancer patients. Thus, ghrelin agonists, such as anamorelin, that basically act on food intake, non-steroidal selective androgen receptor modulators (SARMs), such as enobosarm, hold promise as a new class of anabolic therapies for cancer patients that manifest muscle wasting. In addition, beta-blockers can reduce body energy expenditure and improve efficiency of substrate utilization. Some of them do combine many different pharmacological effects. For instance, espidolol is a non-specific β_1/β_2 adrenergic receptor antagonist that exhibits effects through β and central 5-HT_{1a} receptors to demonstrate pro-anabolic, anti-catabolic, and appetite-stimulating actions. Finally, myostatin antagonists, such as bimagrumab or BYM338, seems to be able in pre-clinical models to prevent skeletal muscle mass loss and preserve muscle function facilitating the recovery from muscle atrophy. All of the commented drugs are certainly new promising strategies to fight cancer cachexia [1].

However, in order to improve the treatment of cancer cachexia, several considerations have to be made. First, a better understanding of the pathophysiological mechanisms related to skeletal muscle and, in general, body wasting, will enable the development of novel therapeutic approaches. Second, more research should also be devoted to biomarkers for cancer cachexia. Indeed, in many clinical centres, cancer cachexia is treated only when a significant amount of weight loss is detected, or when the patients suffer from certain limitations in daily living activities. Biomarkers could detect the changes before any clinical manifestations arouse, facilitating treatment and, possibly, improving prognosis. Progress has certainly been made concerning biomarkers [2] but more research is needed in this field to find an easy measurable --either blood or urine present and specific muscle wasting biomarker. Third, since cancer cachexia leads to decrease potential for muscle regeneration due to the fact that satellite cells are not able to differentiate into myocytes, one new revolutionary concept that will, no doubt, involve further research is that of cell reprogramming to muscle. Therefore, future studies are needed on the potential of stem cell therapy to overcome the problem of muscle cell regeneration. While adult stem cells are tissue-specific and have limited capacity to be expanded *ex-vivo*, pluripotent stem cells, have the capacity to differentiate into any cell type while possessing unlimited *in vitro* self-renewal. Scott et al. [3] described a methodology for large-scale isolation of satellite cells from skeletal muscle. This could then be applied as a therapeutic strategy to stimulate muscle regeneration. Fourth, it is quite clear that a single drug treatment is not an

appropriate approach for the treatment of muscle wasting and, in general, cancer-associated cachexia. During the last years, it has become very clear that combinations of nutrition, nutraceuticals and drugs is a much preferred therapeutic approach. In fact, the approach has to be multimodal involving, not just the combinations mentioned, but also incorporating sustainable exercise. Although this multimodal approach may be difficult to undertake into clinical practice, a case-based approach has recently been published [4]. Muscaritoli et al. [5] have defined the so-called TARGET approach which is a good way of interpreting the multimodal approach. It actually integrates active interventions and research programs related with the onset and progression of cancer cachexia. This approach includes Teaching (nutrition, metabolic alterations in cancer), Awareness (of the negative impact of cancer cachexia), Recognition (diagnosis and staging), Genetics (inherited susceptibility), Exercise (physical activity) and Treatment. The MENAC (Multimodality Exercise/Nutrition Anti-inflammatory treatment for Cachexia) trial [6] also represents a good example of a multimodal approach. This on-going phase III trial is enrolling both lung, cholangio- and pancreatic carcinoma cancer patients and includes nutritional counselling, oral nutrition supplementation (including EPA), a physical exercise program and an anti-inflammatory (ibuprofen) treatment. And finally, the other key aspect to consider is the design of appropriate trials. Indeed, on-going trials have a rather heterogeneous design and include an excessively wide span of different types of tumours with different degrees of cachexia. In fact, a unified approach is requested in a recent consensus document [7]. Some of the most promising drug candidates are completely new molecules and, therefore, particular attention has to be focused on safety issues and not just side effects, but also long-term treatment associated problems, together with the issue of interaction with other drugs. This last point is particularly relevant since, as we have mentioned, the ideal treatment for cancer cachexia is multimodal, involving different drugs and nutraceuticals. Endpoints particularly primary are also something absolutely essential. Lean body mass or, even better, muscle mass together with a measurement of function, like total daily physical activity, are good candidates.

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