

Cachexia: looking yet not seeing

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Cachexia is slowly becoming a relevant issue among healthcare professionals, even among those not directly involved in nutritional care. An example is given by the recent article published by *Nature* during the 8th cachexia Conference (Paris, 4–8 December 2015; society-scwd.org) which highlights this emerging interest of oncology clinicians and researchers.¹ Nevertheless, a long road still needs to be travelled, because major discrepancy exists between what we should do to treat and prevent cachexia and what is actually done in the real life of cancer patients. So, which is the gap still to be filled before cachexia prevention and treatment could be considered standard of care? And more importantly, will ever cancer cachexia treatment become a refundable therapy?

Cancer cachexia is a metabolic syndrome which heavily impacts on nutritional status.² There is now general consensus that cachexia is a negative prognostic factor in cancer patients. In contrast, whether nutritional support yields to better clinical outcome by improving nutritional status remains a debated issue.³ Indeed, available literature does not allow for definitively assessing when, for how long and which type of nutritional support is effective in reducing morbidity, improving mortality and enhancing quality of life of cancer patients. But this absence of evidence does not justify withdrawal or withholding of nutrition therapy in cancer patients. It is recognized that 'adding calories doesn't reverse cachexia',¹ yet without adequate amount of calories and proteins no drug may effectively work against cachexia.

When facing a cachectic patients, it really seems that we look at his/her emaciation and the molecular pathways involved, but we do not see his/her need of calories and proteins. Indeed, the role of nutrition support in preventing or treating cancer cachexia is frequently ignored or overlooked, whereas targeting wasting-related molecular pathways is receiving scientific interest and funding priority. Therefore, whether cancer patients might be able to meet energy and protein requirements is rarely considered when devising a clinical trial.⁴ Unfortunately, this attitude may contribute to the disappointing results obtained in investigating anti-cachexia drugs.¹ In fact, amino acid restriction, as it

occurs in cachectic patients with reduced food intake, robustly activates proteolysis to preserve translation, independently of the use of anti-catabolic drugs.⁵ Early integration of targeted drug therapies and effective management of symptoms reducing energy and protein intake appear a promising strategy to preserve nutritional status, and to enhance the efficacy of anticancer therapies.⁶ In fact, cachexia is a cancer-related syndrome, and consequently its best treatment is the effective oncological management. However, because cachexia influences the delivery of chemotherapy and radiotherapy,⁷ it should be targeted during anticancer treatment, and not considered when the tumour has become unresponsive to treatment. Corie Lok in *Nature* is right that cachexia is seen in the latest stages of the disease,¹ but it may develop years before the tumor is diagnosed.⁸ In this regard, concurrent oncological management, i.e. targeting the tumour while concurrently addressing patient centred needs (i.e. weight loss, fatigue, pain, depression, etc.), has been already proved to significantly increase survival of patients with advanced disease.⁹ It is now time to consider cachexia not only a target to enhance the quality of life of terminally advanced cancer patients, but an opportunity to enhance the response to anticancer treatments.

By targeting clinical outcome rather than nutritional status, it is likely that nutrition care will receive acknowledgement as an important pillar of palliative and concurrent care. But, will this make nutritional support a refundable treatment? Increased longevity and extrinsic factors will bring more and more cases of cancer,^{10,11} a relevant proportion of them being diagnosed at an advanced stage. Cancer is an elusive disease, and current chemotherapy and radiotherapy already showed their limits. Combination of immune therapies has been already proposed to prevent the development of cancer cell resistance.¹² The cancer market is expected to drain large economic resources at an impressive pace and to reach more than 110 US\$ billions in 2024.¹³ In this alarming scenario, results of adequately powered, homogeneous, clinically, and nutritionally oriented trials will be eagerly needed, to enhance the efficacy of anticancer treatments and

their cost-effectiveness. Then, is it so naïve to dream of combination therapies including drugs targeting molecular targets and nutritional strategies to preserve adequate energy and protein intake?

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Conflict of Interest

Prof. Laviano has received honoraria for independent lectures at nutrition industry sponsored scientific and educational events.

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