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Request for regulatory guidance for cancer cachexia intervention trials


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Rome was not built in a day. Likewise, if one considers the evolution of systemic anti-cancer treatment, it took decades to go from acceptance of any therapy at all to single agents achieving isolated tumour responses (without prolongation of survival) to the current use of combination regimens as adjuvant therapy to surgery. Such incremental progress has led to improved quality of life and eventually survival for patients with some types of cancer.

Cachexia and skeletal muscle wasting in cancer are significant clinical problems of high medical need for a large proportion of cancer patients and associated with very poor quality of life and very high mortality.1,2 An effective treatment of a complex multifactorial syndrome such as cachexia will likely evolve from a series of steps of discovery and new interventions before a comprehensive multimodal strategy can be identified that improves patient’s quality and quantity of life.3

There are reasons to be optimistic about the possibility that in the future, cachexia may be treated effectively. A number of drugs have already been developed that target key underlying mechanisms, namely, reduced food intake and altered metabolism and regulation of muscle mass, with the latter being split into pro-anabolic and anti-catabolic approaches. However, there is also a reason to be concerned because of the wide variability in current trial design, including different inclusion criteria, endpoints, analysis plans and the definition of best concomitant supportive care. Taken to the extreme, such differences in general approach have resulted in divergent opinions on what to consider a meaningful clinical endpoint by the European Medicines Agency (EMA) versus the US Food and Drug Administration (FDA). A result has been that in the clinical development programmes of some drugs, different endpoint assessments for American versus European regulatory authorities within the same trials using the same source data have been adopted. An example is the case of the POWER 1 and 2 trials testing the selective androgen receptor modulator enobosarm in patients with cancer suffering from muscle wasting.4–6

There has been a considerable influence from regulatory authorities on trial design. In the last 10 years, some regulatory authorities have consistently suggested that the design of randomized controlled trials testing treatments for cachexia should be aimed at demonstrating appropriate risk versus benefit, where benefit is defined as concomitant improvement in skeletal muscle mass (or lean mass) and relevant/meaningful physical function or improved survival. Whilst this is an admirable goal, from recent phase III trial results, this appears to be possibly unachievable with single modality interventions. Equally, it is not defined to whom the change is supposed to be ‘meaningful’: patient, caregiver, doctor, nurse or healthcare provider? The recent phase III trials of enobosarm used a co-primary end-point of lean body mass and stair climb power.4–6 Based on the FDA agreed
In the related field of COPD-associated body wasting, exercise rehabilitation is well established with extensive guideline recommendations that are evidence-based. These guidelines have been developed over time and are multimodal in focus and are explicitly aimed at improving physical functioning and physical activity levels, nutritional status and quality of life. For patients with heart failure, chronic kidney disease, stroke or age-related frailty, such multimodal approaches are frequently considered, but evidence is so far weak compared with what has been achieved in COPD. Novel therapeutic agents under development for cachexia mostly focus on specific aspects of the syndrome (e.g. muscle anabolism, inflammation or appetite stimulation). Surely, phase III registration trials should assess safety in general, but efficacy specifically in relation to the target of the drug based on its mechanism of action. It may not be right to discard an intervention as ineffective because it does not yet affect a functional outcome, if, in fact – when inserted into a multimodal intervention that reflects the multifaceted aspect of the cachexia syndrome – the drug shows extended benefits that touch on issues such as health-related quality of life, patient-reported symptoms and tolerance of anti-cancer therapy.

In the context of a complex disease process and a desire for multimodal therapies, regulatory advice on co-therapy with nutrition and exercise is also needed. Suggestions as to how best to include in this context supportive care in clinical trials may also be helpful. We understand that this may include additional clinical trials for food products and supportive care approaches and surely this is acceptable, if the rules of the ‘game’ are clear for the good of our patients. Regulators need to be engaged in encouraging the testing of these modalities and their systematic inclusion in trial designs. In heart failure, such activities have already been initiated and aim to shift the development and authorization of medicines from the molecule paradigm to their evaluation in the context of the whole healthcare regimen. If a trial of a new agent incorporates these elements and is successful, it cannot lie with the pharmaceutical company to ensure that such adjuncts are available in precisely the same format everywhere in the world. Rather, the approved drug label may need to recommend such adjuncts for optimal effect.

Clearly, this is not an easy field for new developments, but the medical need is great and the commercial returns for those who make it may be big. Once drugs are approved, the longer process of incorporating new agents into best clinical practice can begin. It should be clear to pharmaceutical companies, academic trialists and regulators that they may need to be more realistic about what can be achieved in a single step. Maybe also the adaptive licensing approach proposed by EMA can help in this process of developing regulatory pathways.

A willingness to consider current data with an open mind and a ‘Notice on Regulatory Guidance’ on cachexia
trial design for cancer and beyond that cuts across continents would be a major step forwards to maintain drug development momentum, if there is to be genuine progress at this exciting juncture in the development of cachexia therapy. We want to help make that a reality whichever way we can.

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Conflict of interest

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