Critical Reviews in Oncology/Hematology 117 (2017) 30–37

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Overcoming obstacles in the design of cancer anorexia/weight loss trials

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Contents

ARTICLE INFO

Article history:
Received 7 March 2017
Received in revised form 30 May 2017
Accepted 21 June 2017

Keywords:
Anorexia
Weight loss
Cancer
Study design

ABSTRACT

Most advanced cancer patients suffer loss of appetite (anorexia) and loss of weight. Despite the fact that cancer anorexia and weight loss are associated with a poor prognosis and detract from quality of life, no interventions have been demonstrated to palliate this syndrome in its entirety, particularly in patients with treatment-refractory malignancies. Recently, two registration trials – one with anamorelin and another with enobosarm – failed to reach their primary endpoints, thus raising questions. Were both these agents ineffective? Alternatively, did study design issues compromise the ability of these trials to identify effective agents? Thus, this review is timely insofar it serves as an introduction to study design, offers guidance on how to test promising agents for cancer anorexia/weight loss, and provides advice for overcoming trial design obstacles.

Our greatest failing is that we neglect the significance of a question and obsess over the accuracy of the answer (Blankinship, 2006).

Such appears to be the case with cancer anorexia/weight loss trials (Fearon et al., 2015). This syndrome of cancer-associated loss of appetite and weight occurs in patients with advanced, incurable cancer and has been described as a "multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass), not fully reversed by conventional nutritional support... leading to progressive functional impairment" (Fearon et al., 2011). Its pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism. Despite the fact that, in patients with advanced cancer, loss of appetite (anorexia) and loss of weight are associated with poor survival and quality of life, the question of how best to treat this syndrome remains unanswered (Dewys et al., 1980; Quinten et al., 2009). A plethora of clinical trials has demonstrated that caloric supplementation is not beneficial for patients with incurable malignancies and, in fact, can be detrimental; indeed, the benefit of nutrition support is confined to a focused group of cancer patients who appear to have highly favorable cancer therapeutic options, as previously reviewed by our group (Jatoi and Loprinzi, 2017). Furthermore, two recent large registration trials, which together

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http://dx.doi.org/10.1016/j.critrevonc.2017.06.008
1040-8428/

enrolled over 1500 patients, failed to achieve their primary endpoints. Such disappointing results underscore the fact that, to date, no intervention has been demonstrated to improve all aspects of the anorexia/weight loss syndrome, particularly in patients with advanced, treatment-refractory malignancies (Baldwin et al., 2012; McGeer et al., 1990).

This therapeutic void has raised concerns that some clinical trials might carry methodological shortcomings that might lead to the premature abandonment of a promising intervention (Fearon et al., 2015). In an effort to curb this possibility, this review serves as an introduction to trial design, offers guidance on testing promising interventions for the cancer anorexia/weight loss syndrome, and provides advice on overcoming obstacles related to designing and completing a clinical trial.

1. A definition

Friedman and others define a clinical trial as a "prospective study comparing the effect and value of intervention(s) against a control in human beings" (Friedman Furberg and DeMets, 2010). This definition emphasizes three obvious but fundamental aspects of a clinical trial. First, a clinical trial is a prospective endeavor. A wealth of important clinical conclusions can be drawn from retrospective studies and even from re-analysis of prospectively-acquired data. However, conducting a study prospectively makes it a clinical trial, and this forward-driven focus serves as an essential design element that helps guard against biased conclusions. Second, a clinical trial tests an intervention that requires a comparative assessment of outcome. Of note, although antineoplastic trials typically involve a drug as the intervention, cancer anorexia/weight loss trials can include non-pharmacologic interventions, such as exercise, dietary modification, or educational programs. All these interventions, no matter what type, entail a comparative assessment when administered within the context of a clinical trial. When referring to a comparative assessment, one often envisions a large phase 3 placebo-controlled trial, which generates the highest level of evidence in support of a change in practice (Burns et al., 2011). However, before the investment in an expensive phase 3 trial, smaller scale, proof-of-concept, or translational trials are often performed to reduce the risk of a failed, larger trial (Table 1). For example, early-stage oncology phase 1 studies are designed to assess adverse events associated with a series of drug dose escalations, as prescribed to very small patient cohorts with each cohort sometimes comprised of less than a handful of patients. Such phase 1 clinical trials often rely on patients' baseline symptoms as the comparative assessment element that serves to determine the final recommended dose of the intervention for future testing. As another example, phase 2 studies, which rely on the dose established in the earlier phase 1 trials, can include one or more study arms and are conducted both to explore the efficacy of an intervention and to further establish the safety of that intervention. Even in a single arm phase 2 trial, a comparative, control element exists, often in the form of historical data. Thus, although the comparative aspect of a clinical trial might not always be readily apparent, it does exist and serves as an inherently important aspect of the trial design. Finally, by virtue of the word "clinical" in "clinical trial,ḣuman beings must be the participants. The evolving role of xenograft or organoid models in clinical research might one day result in a modification of the above definition, but, for now, all high quality, practice-changing evidence requires that human beings be the clinical trial participants (Weroha et al., 2014).

The foregoing definition of clinical trials illustrates the broad-based, incremental approach of drug/intervention development, as reflected in trial design. As noted, clinical trials are categorized as phase 1, 2, and 3 (Table 1). (Phase 4 trials which provide post-marketing data for approved drugs are not discussed here.) Although clinicians await the results of phase 3 trials because of their potential to change clinical practice, the development plan for a therapeutic intervention entails a methodical, stepwise series of clinical trials that often span each of the above development phases, the earlier ones of which often serve to inform the design of the late-stage, phase 3 trial. This effort-intensive approach explains why, for expediency, phases of trials are sometimes merged; for example, phase 1 and 2 trials sometimes take place in sequence within the context of a single, larger clinical trial or, at the very least, an expansion cohort follows the dose escalation cohorts (Iasonos and O'Quigley, 2016; Iasonos and O'Quigley, 2015). This laborious approach also explains why drug-based interventions can take 10 or more years to establish their efficacy, why many are abandoned prior to phase 3 testing, and why the vast majority are never approved for clinical use (CBRA, 2017)

Although the foregoing paradigm of a development plan is drawn from oncology drug trials, this same approach remains relevant to cancer anorexia/weight loss trials. Although some investigators have suggested that trials for the cancer anorexia/weight loss syndrome are distinctly different because of the widely encompassing presentation of this syndrome, we contend that the similarities between the latter and cancer therapeutic trials far outweigh the differences: commonly, cancer therapeutic trials assess tumor response, tumor stability, patient symptomatology, quality of life, patient survival, and biologic endpoints – in a manner that is analogous to trials aimed at treating the cancer anorexia/weight loss syndrome. Any intervention to treat this syndrome requires scientific justification for the dose of the intervention from a phase 1 trial, further confirmation of the safety of the intervention and preliminary evidence of efficacy within the context of a phase 2 trial, and powerful comparative evidence of efficacy as derived from a phase 3 trial. Exceptions occur. For example, the initial studies which

Table 1
United States' National Cancer Institute Clinical Trial Definitions*.

TYPE OF TRIAL	QUOTED DEFINITION
Phase 1	The first step in testing a new treatment in humans. A phase I study tests the safety, side effects, best dose, and timing of a new treatment. It may also test the best way to give a new treatment (for example, by mouth, infusion into a vein, or injection) and how the treatment affects the body. The dose is usually increased a little at a time in order to find the highest dose that does not cause harmful side effects. Phase I clinical trials usually include only a small number of patients who have not been helped by other treatments. Sometimes they include healthy volunteers.
Phase 2	A study that tests whether a new treatment works for a certain type of cancer or other disease (for example, whether it shrinks a tumor or improves blood test results). Phase II clinical trials may also provide more information about the safety of the new treatment and how the treatment affects the body.
Phase 3	A study that tests the safety and how well a new treatment works compared with a standard treatment. For example, phase III clinical trials may compare which group of patients has better survival rates or fewer side effects. In most cases, treatments move into phase III trials only after they meet the goals of phase I and II trials. Phase III clinical trials may include hundreds of people.
Phase 4	A type of clinical trial that studies the side effects caused over time by a new treatment after it has been approved and is on the market. These trials look for side effects that were not seen in earlier trials and may also study how well a new treatment works over a long period of time. Phase IV clinical trials may include thousands of people. Also called post-marketing surveillance trial.

* All definitions are quoted from the NCI Dictionary of Cancer Terms (https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45835; last accessed January 14, 2017).