Contemporary Clinical Trials Communications 12 (2018) 1–8

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

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

Master protocol trials in oncology: Review and new trial designs

Akihiro Hirakawa[a,*], Junichi Asano[b], Hiroyuki Sato[b], Satoshi Teramukai[c]

[a] Department of Biostatistics and Bioinformatics, Graduate School of Medicine, The University of Tokyo, Tokyo, 113-8654, Japan
[b] Biostatistics Group, Center for Product Evaluation, Pharmaceuticals and Medical Devices Agency, Tokyo, 100-0013, Japan
[c] Department of Biostatistics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, 602-8566, Japan

ARTICLE INFO

Keywords:
Master protocol
Basket
Umbrella
Platform
Bayesian adaptive method

ABSTRACT

In oncology, next generation sequencing and comprehensive genomic profiling have enabled the detailed classification of tumors using molecular biology. However, it is unrealistic to conduct phase I–III trials according to each sub-population based on patient molecular subtypes. Common protocols that assess the combination of several molecular markers and their targeted therapies by means of multiple sub-studies are required. These protocols are called “master protocols,” and are drawing attention as a next-generation clinical trial design. Recently, several reviews of clinical trials based on the master protocol design have been published, but their definitions of these such trials, including basket, umbrella, and platform trials, were not consistent. Concurrently, the acceleration of the development of new statistical designs for master protocol trials has been underway. This article provides an overview of recent reviews for master protocols, including their statistical design methodologies in Oncology. We also introduce several examples of previous and on-going master protocol trials along with their classifications by some recent studies.

1. Introduction

In oncology, next generation sequencing and comprehensive genomic profiling have enabled detailed classification of tumors using molecular biology. With this development, targeted therapies are being established for some tumor types based on genetic mutations [1–9]. If patient groups of the same tumor type (for example, gastric, lung, breast, or colorectal cancer) are classified by molecular subtypes, such as by genetic mutation, then patient groups can be further subdivided into unique subgroups. However, it is unrealistic to conduct phase I–III trials according to each subpopulation [10–12]. Common protocols that assess the combination of several molecular markers and their targeted therapies by means of multiple sub-studies are required for single and/or multiple tumor types. These protocols are called “master protocols,” and are drawing attention as a next-generation clinical trial design.

Three challenges that have been particularly difficult in common clinical trials are possibly alleviated by conducting multiple clinical trials based on a master protocol [13]. First, inter-patient and intra-patient heterogeneity can be evaluated efficiently [14]. Identical tumor types can exhibit different responses to treatments depending on patient characteristics or disease stage, and even within the same patient, differences in the type of cancer cells within the tumor tissue can also generate a different treatment response. In trials using a master protocol, trial data from multiple sub-studies can be comprehensively used to evaluate inter- and intra-patient heterogeneity. Second, findings on specific signal pathways strongly associated with driver gene mutations and cancer cell growth and progression can be obtained [15–17]. Third, combining two or more targeted therapies makes it possible to expand the genetic mutations being studied [18–20].

This article begins with an overview of the history from biomarker-based trial design to master protocol trial, and subsequently summarizes clinical trials using master protocols in oncology based on recent general theories of master protocol design [21–23]. We introduce several examples of master protocol trials along with their classifications according to previous studies. We also discuss new statistical designs for basket trials, including designs that use the recently developed response-adaptive randomization, in addition to discussing the future direction of master protocol trials.

2. Changes from biomarker-based to master protocol trial design

In order to understand the motivation and concept of clinical trial design using a master protocol, we first introduce the clinical trial designs that use molecular markers, along with their history in cancer treatment. In oncology, patients are generally classified by their primary cancer and stage, and randomized controlled trials are conducted

* Corresponding author. Department of Biostatistics and Bioinformatics, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8654, Japan.
E-mail address: hirakawa@m.u-tokyo.ac.jp (A. Hirakawa).

https://doi.org/10.1016/j.conctc.2018.08.009
Received 20 April 2018; Received in revised form 10 August 2018; Accepted 23 August 2018
Available online 24 August 2018

for each patient population to create standard therapies. Historically, cytotoxic agents have been develop based on this perspective. However, research and development in the 2000s enabled cancer cell growth and progression to be defined at cellular and molecular levels, and the presence or absence of molecular markers or genetic mutations enabled classification of particular tumor types into several subtypes. At the same time, there were developments in the chemotherapeutic drugs available, shifting from treatments centered on cytotoxic agents to those using molecularly targeted agents, which act selectively on cancer cells. Recently, there is active research on immune checkpoint inhibitors, which attack cancer cells by utilizing a patient's immune response. Molecularly targeted agents that target specific molecular markers include gefitinib and erlotinib for *EGFR* gene mutation-positive inoperable, recurrent, or metastatic non-small cell lung cancer [5,24], as well as crizotinib, alectinib, and ceritinib for *ALK* fusion gene-positive non-small cell lung cancer [6–8,25]. Immune checkpoint inhibitors presently include nivolumab and pembrolizumab [26,27].

Clinical trial designs based on molecular markers began to gain popularity with the aforementioned changes in chemotherapy agents. Trial designs called “enrichment designs” or “targeted designs” are studies where patient populations with a single molecular marker for which a drug's effects can be expected in a specific tumor type (in this paper, we will assume that it is effective for the marker-positive population). This design is selected on the premise that: i) the molecular marker is an established marker, which is strongly correlated with the efficacy of an investigational drug; ii) it has been biologically demonstrated that drug efficacy cannot be expected in the marker-negative cases; and iii) that a diagnostic tool for evaluating molecular marker status has been developed. Clinical trials using the enrichment design have included a clinical trial of trastuzumab [1], the N9831 trial for *HER2*-positive breast cancer [28], and the ToGA trial on *HER2*-positive stomach cancer [11]. If the molecular marker is not established as a reliable marker, the use of a marker-stratified design may be considered. In this design, patients were assigned to arms by molecular marker positivity or negativity, and were randomized within each arm. Clinical trials that used the marker-stratified design include the INTEREST [29] and MARVEL [30] trials. After this type of design was introduced, sequential subgroup-specific, marker sequential test (MaST) and fallback designs were proposed as extensions of the marker-stratified design [31]; this eventually led to the proposal of clinical trials that use the master protocol design.

3. Master protocol trial

3.1. Definition and characteristics

A master protocol is a comprehensive protocol created for evaluating multiple hypotheses of sub-studies that are concurrently conducted. This comprehensive protocol comprises different sub-protocols of multiple concurrently-operating sub-studies (Fig. 1), where the sub-studies are commonly conducted on populations based on specific tumor types, histologic types, and/or molecular markers. We will refer to these types of trials as “master protocols.”

A master protocol trial uses a common system for patient selection, logistics, templates, and data management [22]. Histologic and hematologic specimens of patients enrolled in master protocol trials are also measured and analyzed using a common basic system (e.g., next generating sequencer and immunohistochemistry) to collect coherent molecular marker data. Patients can participate in sub-studies for which they meet eligibility criteria based on their molecular marker data. Thus, enrolling in a master protocol trial increases the chance of participation in a trial that is most suitable for a given patient. Even if there are no sub-studies that a given patient can participate in, they will be followed-up, and can be placed on a waiting list until an appropriate sub-study is started. Furthermore, natural history data from a waiting-list can be used as controls in evaluating the efficacy of an investigational drug in a single-arm sub-study.

3.2. Trial purpose

Master protocol trials can be exploratory or confirmatory [10,32–34]. Exploratory master protocol trials are often composed of multiple single-arm sub-studies, and confirmatory master protocol trials are composed of multiple randomized sub-studies. For either trial type, the design and statistical considerations are commonly standardized between all sub-studies.

3.3. Advantages and challenges

The advantages of a master protocol trial are related to the fact that they include data from sub-populations on a broad range of molecular markers. In comparison with the marker-based trials described in Section 2, two advantages appear in the master protocol trials. First, this enables efficient enrollment of rare fraction patients so that centralized patient management, based on a common protocol, promotes the acceleration of clinical development. Second, master protocol trials are beneficial for patients as well because they increase the chance of trial participation for which they can expect optimal therapeutic effects. On the other hand, the challenges associated with master protocol trials, include the fact that several small sub-studies are being conducted in parallel, which may increase the rate of false positive findings.

4. Basket, umbrella, and platform trials

4.1. Definitions

A master protocol trial is often classified into basket, umbrella, and platform trials based on characteristics of the study population (e.g., disease, histologic type, molecular marker) and on both the type and number of study therapies. The common definitions of each trial type based on literature [22,23] are shown in Table 1. However, as pointed out by Renfro and Sargent [23], the definitions of each trial type are not standardized [10,20,35–37], with possible overlaps between them that should be noted. For example, the NCI-MATCH trial, which will be mentioned in a later section, is a type that has aspects of both basket and umbrella trials. In this article, we will organize the trial types by definitions given in recent works [21–23].

4.2. Basket trials

A basket trial evaluates one targeted therapy on multiple diseases or multiple disease subtypes. In oncology, this is exemplified by examining the therapeutic effects of molecularly targeted agents for several tumor types that may have a common single molecular marker, or genetic mutation, by tumor type and/or across tumor types (Fig. 2). In this scenario, the grouped tumor types form a basket, and sub-studies are conducted by tumor groups within it. Basket trials are often conducted as single-arm, phase II trials with the purpose of evaluating proof-of-concept (POC) in an early stage of development. Generally, the number of participants in individual sub-studies are between 20 and 50, and hypotheses that can demonstrate statistical significance are made only when there is major therapeutic efficacy; therefore, a basket trial is considered a “signal-finding” trial. As for sub-study design, two-stage or multi-stage designs may be used. As such, basket trials are characterized by the comprehensive execution of single-arm trials with a small number of patients, which enables efficient patient enrollment for rare cancers or rare fractions. However, it should be noted that basket trials have the assumption that they allow a fairly accurate prediction of whether a tumor with particular molecular characteristics will respond to a targeted therapy; furthermore, such response to a targeted therapy is established irrespective of the histologic type of the tumor. Moreover,