The Master Protocol Concept

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During the past decade, biomedical technologies have undergone an explosive evolution—from the publication of the first complete human genome in 2003, after more than a decade of effort and at a cost of hundreds of millions of dollars—to the present time, where a complete genomic sequence can be available in less than a day and at a small fraction of the cost of the original sequence. The widespread availability of next-generation genomic sequencing has opened the door to the development of precision oncology. The need to test multiple new targeted agents both alone and in combination with other targeted therapies, as well as classic cytotoxic agents, demands the development of novel therapeutic platforms (particularly Master Protocols) capable of efficiently and effectively testing multiple targeted agents or targeted therapeutic strategies in relatively small patient subpopulations. Here, we describe the Master Protocol concept, with a focus on the expected gains and complexities of the use of this design. An overview of Master Protocols currently active or in development is provided along with a more extensive discussion of the Lung Master Protocol (Lung-MAP study).
Semin Oncol 42:724-730

The paradigm for developing new cancer therapeutics is undergoing an evolutionary shift of substantial magnitude not witnessed since the incorporation of the randomized clinical trial (RCT) as the gold standard benchmark for therapeutic progress. The advent of the RCT is rooted in the post-war antibiotic era of the late 1940s and saw its first application in oncology in the 1960s. Since that time, it has been used as the ultimate level of evidence supporting the clinical application of specific therapeutic interventions. Over the past half century, the RCT has been the platform upon which advances in cancer have been tested primarily through a multidisciplinary approach combining various systemic agents along with optimal radiation and surgical techniques delivered to populations of patients with similar stages of a particular cancer type defined by its organ of origin. There is no question that this approach has resulted in substantial improvements in outcomes for patients with various cancers. However, particularly in patients with common cancers of solid organs, advances have been tedious, incremental and often associated with significant toxicities related to the collateral cellular damage to normal tissues resulting from the nonspecific nature of classic cytotoxic agents.

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This work was supported in part by PHS/DHHS/NIH grants no. CA180888 and CA180819 awarded by the National Cancer Institute (NCI), National Clinical Trials Network (NCTN).
Conflicts of interest: none.
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0093-7754/ - see front matter

http://dx.doi.org/10.1053/j.seminoncol.2015.07.009

only a small fraction of the total patient population with a cancer arising from any particular organ. For example, in patients with adenocarcinoma of the lung, only about 15% will have a mutation in the epidermal growth factor receptor (EGFR). Thus, targeting this receptor will result in significant clinical benefit with modest toxicities in only a small fraction. Using classic clinical trials methods would require the screening of at least six patients to identify one patient who may be eligible for and ultimately consent to participation in a clinical trial investigating a new EGFR inhibitor, thus resulting in a marked increase in time, resources, and funding to accrue to even a modest size trial.

In parallel with the advances in "omic" technologies has been an ever-increasing understanding of the cellular pathways that underpin the dysregulated growth and spread of malignant cells. New appreciation of the specific proteins responsible for cancer growth has led to an intense effort on the part of academic investigators and industry to discover and develop a multitude of small molecules capable of interacting with and inhibiting the function of many intracellular proteins constitutively activated as a result of genetic alterations. It has become evident that the various intracellular pathways responsible for cellular proliferation are extremely complex with redundant pathways, feedback loops and multiple points along any given pathway that may be activated or suppressed by numerous cellular proteins. The realization of this complexity and early clinical evidence with the use of single targeted therapeutics has led to the widely accepted hypothesis that it is highly likely that more than a single targeted therapeutic will be needed to affect a long-term clinical benefit.

The parallel availability of highly multiplex technologies along with the need to test multiple new targeted agents both alone and in combination with other targeted therapies as well as classic cytotoxic agents demands the development of novel therapeutic platforms (eg, Master Protocols) capable of efficiently and effectively testing multiple targeted agents or targeted therapeutic strategies in relatively small patient subpopulations. To this end, a number of platform clinical trials have been spawned with the short-term goal of identifying active agents and strategies in molecularly defined patient subpopulations. The idea of creating a platform such as a Master Protocol to gain efficiencies is not a new one, but it has not been until this era of targeted therapies that the true potential of this concept has been appreciated.

THE MASTER PROTOCOL CONCEPT

The general goals of a Master Protocol are to improve genomic screening efficiency and to increase the speed of drug development and evaluation. Screening efficiency is improved by subjecting the tumors of a large number of patients to assays capable of identifying abnormalities in multiple potential targets, reducing the screen failure rate by both ensuring a sufficient amount of a patient's specimen is submitted for screening multiple biomarkers and by screening patient specimens using a common platform or set of assays to evaluate for the candidate biomarkers. Such a strategy is designed to provide a sufficient "hit rate" for biomarker-driven studies to allow enrollment of a substantial percentage of the screened patients into clinical trials, thus promoting the engagement of patients, physicians and drug sponsors. The speed of drug development and evaluation is increased by providing an infrastructure to open and close studies of new agents and biomarkers more quickly. In general these types of studies also increase the speed of development and evaluation by looking for "large effects" and therefore requiring fewer enrolled patients per trial. Finally, with the use a common platform/design a Master Protocol can also facilitate US Food and Drug Administration (FDA) approval of new drugs and bring safe and effective drugs to patients faster.

The general design for a Master Protocol is presented in Figure 1. This Figure depicts the general idea of a Master Protocol, which is to provide a platform for simultaneously evaluating multiple agents in patients with specific genetic abnormalities that may be targeted by the agent under investigation. Patient specimens are evaluated for the set of biomarker/biomarker assays and then on the basis of this evaluation are assigned to a sub-study within the Master Protocol. The sub-studies may have a common design or the designs may vary across the biomarker/biomarker assay groupings and the platform may or may not include a sub-study for patients who are not eligible for any of the biomarker-driven studies.

The benefit to including a "non-match" study is to maximize the opportunity for clinical trial enrollment for all screened patients. However, depending on the disease setting under study, there might not be a reasonable choice for a "non-match" study. Moreover, while the biomarker-driven sub-studies may be set up for FDA approval of the drug, the undefined and potentially changing nature of the "non-match" population may not be as clear for FDA approval.

A benefit to use of a common design across sub-studies is operational efficiency, development and approval of the sub-study design occurs generally once and also allows for standardization across the studies. However, use of a common design requires some level of common criteria or evidence around the biomarker/biomarker assay and investigational therapy for use in the Master Protocol. Varying