

Oncology Drug Development: What Is Changing?

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Drug development is a long and expensive process that, on average, takes about 13 years from drug discovery to approval by the U.S. Food and Drug Administration (FDA) for patient use (IMS Health, 2004). Cancer drugs cost more to develop than other types of drugs because of the absence of preclinical systems that can accurately predict the efficacy and toxicity of new agents and the increasing complexity of clinical trials that involve molecularly targeted agents and advanced technologies (Kummar, 2007). Developing a new cancer drug is estimated to cost \$1.042 billion compared to \$848 million for other drug types (DiMasi & Grabowski, 2007). Data from 1991–2000 show that only about 5% of potential cancer drugs are approved for patient use (Kola & Landis, 2004) (see Figure 1). This high rate of failure in cancer drug development compounded by the high cost of research has set the stage for a new approach in developing cancer drugs: phase 0 trials.

Historical Overview

The drug development process involves multiple steps. Preclinical studies are performed in the laboratory setting with animal models and, if promising, may then be tested in humans. Clinical trials study new drugs or a combination of drugs in human subjects. A clinical trial generally has three distinct phases before approval is granted by the FDA for use in the general population. A clinical trial may occasionally have only two phases, usually when the drug being developed is for a rare disease.

Phase I trials test an investigational agent in a small number of patients

(about 15–40). The objective is to evaluate the maximum tolerated dose (i.e., the maximum dose of study drug that can be tolerated without significant risk of severe side effects) (Oncology Nursing Society, 2001).

Phase II trials test investigational agents in a larger group of patients (about 100–300) with a similar diagnosis (e.g., all patients enrolled in a trial have stage III lung cancer). Most patients enrolled in a phase II trial have received standard therapy for their disease and either had progression of the disease or saw no response. The objective is to evaluate and assess the disease response to the drug and further examine the drug's safety profile.

In phase III trials, the experimental agent or treatment is given to a larger number of patients (about 1,000–3,000) to evaluate the responses of the new treatment compared to standard or conventional care and to continue to collect data regarding side effects and long-term sequelae (Kummar, Gutierrez, Doroshow, & Murgo, 2006).

Most potential new cancer drugs are found to be either too toxic or ineffective. Data from 2000 show that 25% of all cancer drugs fail because of toxicity and 30% fail from ineffectiveness (Kola & Landis, 2004) (see Figure 2). Unfortunately, most potential cancer drugs fail late in the process, in either phase II or phase III. In addition, 25% of potential cancer drugs are not approved by the FDA after all three phases of clinical trials are completed (Kola & Landis); therefore, total

cost of research and development has been incurred with no benefit.

Changing Approaches to Drug Development

A shift has occurred in the development of new cancer treatments. The standard of care since the 1960s has been chemotherapy, which involves nonspecific cytotoxic agents. Chemotherapy destroys dividing cells, targeting cancer cells and normal cells at the same time. Because of advancements in genetic and molecular biology, agents have been developed that focus on a specific molecular target (Collins & Workman, 2006). Herceptin, an example of this new type of agent, is used in patients with breast cancer who have tumors with higher than normal levels of the HER2 protein on the surface of the cancer cells, prompting cancer cell growth. Herceptin works by bonding to the HER2 protein (also known as a receptor) so that the cancer cells are no longer stimulated.

This shift in focus toward more targeted therapies combined with rising costs of research and development for cancer agents has resulted in a re-evaluation of the drug development process by the FDA. In 2004, the FDA published *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*, which acknowledged a recent slowdown in “innovative medical therapies reaching patients.” According to the FDA (2004), medical product

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