Balancing the Need for Quick Cures With Independent Research Oversight

BY JOHN E. STEINER JR., ESQ., CHC, CCEP AND MAURIE MARKMAN, M.D.

John E. Steiner Jr., Esq., CHC, CCEP, is chief compliance officer at the Cancer Treatment Centers of America, Schaumburg, Ill.

Maurie Markman, M.D., is vice president for patient oncology services and national director for medical oncology at CTCA.

Introduction and Purpose

One purpose of this article is to provide a perspective on the debate about the balance between the two interrelated goals of medical research and advancing the diagnosis and treatment of diseases. One goal is to speed up advances in medical breakthroughs and make those available to patients. Those efforts are especially powerful in the private sector. The other goal is to provide some degree of independent oversight, usually at the federal level, of medical research efforts. This is a delicate balance and requires continuous, healthy debate.

Another purpose of this article is to illustrate how important focused, operational efforts are for the successful implementation of medical advances.

Examples are provided below of various cancer treatment services currently provided by Cancer Treatment Centers of America (CTCA). Those examples highlight aspects of the debate, with priority placed on what is best for cancer patients. By illustrating what can be done to bring innovations to patients, the authors hope to contribute to the “sense of urgency” that policymakers and agency decisionmakers should maintain in their analyses of coverage and payment choices for medical services.

This Perspectives article closes with thoughts related to recent funding for “comparative effectiveness” research and what we should expect, both as patients and
as a country, from the sustained “search of urgency” for effective disease treatments.

**A Sense of Urgency**

Global efforts continue relentlessly to compress the time gap between basic research and medical advances that help patients. Increasingly, one hears or reads about accelerating “bench to bedside” research in numerous clinical areas, especially cancer. By way of context, most observers agree that knowledge advances in basic sciences (e.g., microbiology, cell biology, immunology, etc.) are roughly seven to 17 years ahead of application of that knowledge in the medical arena.

In 2006, the National Institutes of Health fundamentally changed its research grant awards procedures. A national consortium of medical research institutions now are funded by Clinical and Translational Science Awards (CTSA). The goal is to create 60 funded Centers for Clinical and Translational Science via these awards (see [http://www.ctsaweb.org](http://www.ctsaweb.org)). In turn, the goal of these grant recipients is to accelerate “bench to bedside” advances for patients.

Consistent with the theme of a “sense of urgency,” summarized below is one example of a regulatory approach to expedite drug approvals by the Food and Drug Administration (FDA). The FDA serves to filter and control ideas and innovation in the perceived best interests of the public. That role can be beneficial for the public. There is not a level field for the public’s general knowledge and understanding of disease processes and the medical expertise of institutions and individuals who try to address those diseases processes. In short, that is why the FDA must focus on “safety and efficacy” of drugs and devices over which it has jurisdiction.

While there are inherent limits to the responsiveness of large organizations, such as the FDA, it is encouraging to highlight an example of the FDA’s demonstrated flexibility in addressing the interests of patients with serious diseases. The range of “serious diseases,” as identified by the FDA includes cancer, heart failure, AIDS, and Alzheimer’s.

The FDA has three separate approaches to making drugs available as rapidly as possible to treat serious diseases:

- priority review;
- accelerated approval, and
- fast track.1

For the sake of brevity, key points related to the “fast track” approach for drug approval are summarized below. This section also highlights points that may still impede getting help to patients as soon as practicable.

Fast track is a process designed to facilitate the development and expedite the review of drugs to treat serious diseases and fill a previously unmet medical need. The purpose is to get important new drugs to patients earlier. Criteria for “fast tracking” include the drug’s impact on survival, day to day functioning, or, the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

The FDA approach explains that any drug under development to treat or prevent a disease with no current therapy is directed at an “unmet need.” Filling an “unmet medical need” means providing a therapy where none exists or providing a therapy which may be potentially superior to an existing therapy. If there are existing therapies, a fast track drug must show some advantage over available treatment, such as:

- showing superior effectiveness;
- avoiding serious side effects associated with an available treatment;
- improving the diagnosis of a serious disease where diagnosis results in an improved outcome; and
- decreasing a clinically significant toxicity of an accepted treatment.

A drug with “fast track” designation qualifies for different treatment, such as:

- more frequent meetings with the FDA to discuss the drug’s development plan and ensure collection of appropriate data needed to support drug approval; and
- more frequent written correspondence from the FDA about the design of the proposed clinical trials, etc.

These are meaningful advantages that are consistent with accelerating availability of new drugs for patients with serious diseases. However, definitional and process issues remain and continue to impede flexibility for providers and individuals who need to further shorten approval times.

For example, FDA accelerated approval processes, one of the three FDA approaches listed above, hinge on whether a drug is “reasonably likely to predict a real clinical benefit.” This proof is provided through phase IV confirmatory trials. Unfortunately, in the cancer arena it is often difficult to provide a clear definition of “clinical benefit.” While an improvement in survival is always a worthy goal of a new anti-neoplastic drug or novel therapeutic strategy, it is rational to strongly argue that other potential measures of “benefit” should be added to the regulatory approval paradigm. For example, a novel agent that improves distressing symptoms of cancer (e.g., pain) through the shrinkage of existing tumor masses or substantially delays the onset of new debilitating symptoms should surely fulfill the definition of “clinical benefit.”

The agility of smaller, private sector companies, such as CTCA, demonstrates the feasibility of acting with “urgency” to help patients. Over the past several years, CTCA and its physician investigators have provided advanced, innovative therapeutic services to help cancer patients address “unmet medical needs” as quickly as possible. Moreover, CTCA has adopted “lean thinking” to eliminate wasteful practices that could further delay patient treatment and unnecessarily increase costs for payers. Several examples of these clinical and focused, operational efforts are presented below.

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1 [http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccessToImportantNewTherapies/default.htm](http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccessToImportantNewTherapies/default.htm)
Nonetheless, for many patients with stage III and IV cancers, coverage and payment issues still impede or prevent patient access to treatment.

**Intraoperative Radiation Therapy**

CTCA is the first hospital in the United States to house the Novac7, which is the first mobile electron linear accelerator for intraoperative radiation therapy (IORT). IORT was first introduced to the United States in the 1970s. IORT is the delivery of a single, high dose of radiation directly to the tumor bed during surgery. Radiation is directed straight to the target, thereby sparing the normal surrounding tissues as much as possible.

At the time of preparing this article for publication, IORT is provided in only 15 hospitals in the United States. Only 11 hospitals, including CTCA, have a dedicated surgery suite for IORT. Historically, the patient, surgeons, radiation oncologist, anesthesiologist, nurses, and technicians were transported, during surgery, to the bunker of the IORT machine. This put the patient at excessive risk in addition to creating enormous logistical difficulties. The newest innovation in IORT is the development of a mobile machine. Additional benefits of this innovation include fewer individual treatments and better cosmetic results, since there is immediate breast reconstruction. IORT can be used for cancers in the following areas: breast, head and neck, lung, esophagus, stomach, pancreas, rectum, gynecological, prostate, and soft tissue sarcomas.

The innovation process began when a radiation oncologist at CTCA’s Eastern Regional Medical Center, Dr. Pablo Lavagnini, and his team sought to purchase the Novac7. CTCA sought licensing approval from the Pennsylvania Department of Health and Department of Environmental Protection. Despite FDA approval, Pennsylvania state approval was protracted, due in part to the uniqueness of Novac7 in the United States and its origins in Italy. In February 2009, the Pennsylvania regulatory authorities concluded final on-site inspections, and in March 2009 CTCA’s Eastern Regional Medical Center received the amended accelerator license, which now included the IORT. Dr. Lavagnini treated the first patient with IORT on March 9, 2010, and 70 patients have been treated as of March 2011.

CTCA’s efforts to bring IORT to the United States is an example of what can be accomplished when researchers, clinicians, and operations personnel act with urgency to better serve patient needs.

**OVax**

CTCA is engaged in cutting-edge research with a vaccine to treat ovarian cancer. Patients who failed prior chemotherapy regimens increasingly contacted CTCA to find an alternative life-saving solution. CTCA responded in 2008 with the FDA-approved phase I-II trial of the OVax vaccine for patients with advanced, chemotherapy-resistant ovarian cancer. In 2008, Dr. Sybilann Williams, a gynecologic oncologist and surgeon at CTCA’s Midwestern Regional Medical Center (MRMC), and Dr. David Berd, national director of immunotherapy and a medical oncologist at CTCA’s Eastern Regional Medical Center (ERM C), began to enroll patients in this trial at MRMC. The goal is to determine whether a vaccine made from the patient’s own tumor tissue can stimulate an immune response against the patient’s tumor cells. Patients undergo debulking surgery (an attempt to remove all visible tumor within the abdominal cavity) and their tumor tissue is sent to an outside company for production of the vaccine. OVax provides a nontoxic, therapeutic alternative for patients and allows them an eight-week respite from physically taxing therapies such as chemotherapy, which may have debilitating side effects. Eight patients have undergone treatment in this protocol.

**HIPEC**

Dr. Charles Komen Brown of CTCA’s Midwestern Regional Medical Center is one of approximately 20 surgical oncologists in the United States regularly performing the Hyperthermic Intraperitoneal Chemotherapy (HIPEC) procedure. HIPEC is used to treat complex abdominal cancers such as colorectal cancer. This procedure combines the process of hyperthermia with debulking surgery. During the treatment, heated chemotherapy solution circulates inside of the abdominal cavity for 90 minutes directly following tumor debulking surgery. The goal of using heated chemotherapy following debulking is to eliminate any residual tumor cells that reside within the abdominal cavity.

HIPEC allows treatment to reach cancer cells that otherwise are invisible to the naked eye. HIPEC targets existing metastatic and micrometastatic tumor deposits that existed before the patient is brought to surgery and that are not removed by a debulking procedure. The HIPEC procedure holds additional benefits for patient quality of life including the ability to: deliver higher doses of chemotherapy than usually possible with standard chemotherapy delivery; concentrate delivery within the abdomen, minimizing exposure to the rest of the body; and minimize intense chemotherapy side effects. Dr. Komen Brown began HIPEC at CTCA in February 2009 and has since performed approximately 36 treatments.

**Conclusion**

The Patient Protection and Affordable Care Act (PPACA) signed into law on March 23, 2010, could lead to significant advances in clinical research. For example, PPACA provided $3 billion in funding for “comparative effectiveness” research and established the Patient-Centered Outcomes Research Institute to oversee these research initiatives. Members of the institute will include directors from the National Institutes of Health and the Agency for Healthcare Research and Quality, among other appointees.

It is imperative that this group looks to successes in the private market, such as those presented above from the Cancer Treatment Centers of America, when evaluating current research processes and procedures. Comparative effectiveness studies, while well-intended, run the risk of becoming bogged down by agency size and regulatory limitations that may impede sustained, quick progress. Moreover, the PPACA legislation removes annual and lifetime limits to coverage and prevents pre-existing condition exclusions to coverage. Once these provisions fully go into effect for adults, more patients with end-stage cancer will be demanding treatment options, quickly.