Background for the March 2003 Oncologic Drugs Advisory Committee (ODAC) on Accelerated Approvals

Based on laws passed by Congress in 1938 and 1962, applicants submitting New Drug Applications (NDAs) to the FDA are required to demonstrate the drugs to be safe and effective. The safety requirement is derived from the Federal Food Drug and Cosmetic Act of 1938 (FD&C Act). The effectiveness requirement stems from a 1962 amendment to the Act. Subsequent judicial rulings established that effectiveness must be an effect that is clinically meaningful.

What is clinically meaningful is a matter of judgment. Apart from obvious benefits, such as improved survival, a decreased rate of important events (stroke, heart attack), or a beneficial effect on symptoms, drugs have also been approved on the basis of effects on "surrogate endpoints." A surrogate endpoint is a laboratory measure or physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint. The effect on the surrogate is of no value to the patient unless it in fact leads to such a clinical benefit. There are well established surrogate endpoints in cardiovascular medicine, including blood pressure and cholesterol. Both epidemiologic and clinical trial evidence support them. Anti-HIV drugs have been approved based on effects on HIV titers and CD4 counts.

A wide variety of endpoints have been used to establish effectiveness in oncology. Of interest, until 1985, tumor response was the usual endpoint. In that year, an advisory committee including Drs. Moertel and Canellos urged a change, leading to a guideline that called for a measured benefit, i.e., an effect on survival or symptoms. Since then we have, in fact, asked for such benefits, although there have been exceptions. In adjuvant breast cancer, we have accepted an effect on time to recurrence, feeling that delay in learning of persistent tumor was a benefit and that in most cases recurrence was symptomatic. Hormonal treatments for breast cancer have been approved based on response rates, reflecting the low toxicity of these agents (but also, presumably, the view that it is probably generally beneficial to shrink tumors). Also, from time to time, we have relied on increased time to progression as a reasonable predictor of benefit, although the ODAC, when asked, has generally thought this a bad idea. Time to symptomatic progression would be a clearly useful endpoint, but this is rarely measured. We have also accepted durable complete responses as a clinically meaningful benefit, although this has been important principally with leukemias/lymphomas rather than solid tumors (except for testicular cancer).

In 1992, Subpart H was added to the NDA regulations allowing "accelerated approval" for diseases that are serious or life-threatening. Under accelerated approval regulations, for indications where the new drug appears to provide benefit over available therapy, accelerated approval may be granted on the basis of a surrogate endpoint that is "reasonably likely" to predict clinical benefit. The preamble to the rule is clear in identifying this as a lower standard of evidence than would support regular approval based on a surrogate. After approval, the sponsor is required to perform a post-marketing

study (either a new trial or completion of an ongoing trial; the regulations state that "postmarketing studies would usually be studies underway") to demonstrate that treatment with the drug is indeed associated with clinical benefit. If those studies fail to demonstrate clinical benefit or if the sponsor does not show "due diligence," then the regulations describe a process for removing the drug from the market.

In the March 1996, a U.S. presidential document entitled 'Reinventing the Regulation of Cancer Drugs' announced how FDA would apply the accelerated approval rule to new cancer treatments, specifically by basing approval on demonstration of objective tumor shrinkage in patients with refractory disease or whose disease had no useful therapy.

1. For products approved on the basis of tumor shrinkage, post-approval studies will usually be required to further define the utility of the new agent for the approved and/or other indications, either alone or in combination with other agents.

2. For accelerated approval of products that remove treatment-associated toxicities, post-approval studies will be required, as appropriate, to study the effect of the therapy on survival, and/or to demonstrate that the surrogate measures correspond to clinical benefit

3. A post-approval study will not necessarily be required in the exact population for which approval was granted. Where a product was approved to treat patients with refractory malignancy, additional information from that population may not, for example, be as useful as randomized, controlled trials in a previously untreated population.

This initiative has been successful in promoting the early approval of cancer drugs with antitumor activity. From 1992 to 2002, 19 indications for anticancer drugs or biologics have been approved under subpart H. Of these, 4 have been subsequently converted to full approval. Of the remaining 15, seven received accelerated approval recently (within 18 months of issuance of sponsor invitations for this advisory committee meeting), and therefore sponsors for these indications were not asked to present the status of phase 4 commitments. For the remaining 8 indications, individual sponsors will be presenting the status of phase 4 commitments.

The purpose of this meeting of ODAC is to review and discuss past oncology drug accelerated approvals and current progress with the associated phase 4 commitments. Ideas for how the oncology drug accelerated approval process might be improved will also be solicited.

Attachments

1. AA regulations with preamble

2. Reinventing the Regulation of Cancer Drugs

3. Accelerated Approval letters for 8 sponsors that are presenting
   a. Doxil – Kaposi's sarcoma (approved Nov 17, 1995)
   b. Ethyol – reducing renal toxicity assoc. with cisplatin in patients with advanced NSCLC (approved Mar 15, 1996)
   c. Ontak – CTCL (approved Feb 5, 1999)
   d. DepoCyt – lymphomatous meningitis (approved Apr 1, 1999)
   e. Doxil – metastatic ovarian cancer (approved Jun 28, 1999)
   f. Temodar – anaplastic astrocytoma (approved Aug 11, 1999)
   g. Celebrex – reduce the number of adenomatous colorectal polyps (approved Dec 23, 1999)
   h. Mylotarg – AML (approved May 17, 2000)

4. Temple RJ, A Regulatory Authority's Opinion About Surrogate Endpoints. In Clinical Measurement in Drug Evaluation 1995 John Wiley and Sons Ltd.

5. O'Shaughnessy JA et al. Commentary concerning demonstration of safety and efficacy of investigational anticancer agents in clinical trials. JCO 9:2225-2232, 1991.