Dying Patients and Their “Right” to Unapproved Drugs: Did the D.C. Circuit Finally Get It Right in Abigail Alliance?

By Bruce Patsner, M.D., J.D.

The Texas Medical Center in Houston is the largest patient care/medical research complex in the world. On any given day hundreds of patients, many not from Texas, come to institutions such as the M.D. Anderson Cancer Center for treatment of life-threatening diseases for which the standard medical therapies available at home have proven ineffective. Some of the drugs these patients are seeking are experimental and have never been approved by the United States Food and Drug Administration for marketing in the United States.

There are two core questions at hand: (1) what are the existing legal mechanisms cancer patients currently have for access to these unapproved drugs, and (2) do terminally ill patients have a constitutional right to access experimental drugs before FDA has approved them?

Existing Legal Mechanisms

Most of the unapproved drugs in contention here are drugs which are considered Phase I drugs. As a rule, the development of new cancer drugs follows three phases when testing in humans begins (testing in animals, which invariably precedes human testing, is also a requirement for FDA drug approval and is referred to as “Preclinical” testing or Phase 0). Phase I testing is the first testing of a drug in humans and is usually carried out in small (3-6 patients) cohorts of healthy individuals using escalating doses of the drug in order to determine preliminary safety and tolerability data. In other words, at the time of Phase I testing, the lethality of the drug in humans is not known. In part, this is one reason why Phase I testing is usually done in healthy individuals as opposed to terminally ill patients. Once Phase I testing is completed and investigators have some idea how toxic a drug is and what the acceptable doses are, the drug is then tested in larger groups of patients with a variety of different cancers to see if the drug is effective against any of them (Phase 2); efficacy is usually measured by a reduction in the size of the tumor on CT or MRI scans. The drugs which demonstrate effectiveness against certain tumors are then tested against that type of cancer in larger, randomized trials against known therapies (Phase 3). At least one, though usually two, large Phase 3 trials are required by FDA’s new drug approval (NDA) process.1

Testing with Phase I drugs is both dangerous and unlikely to be of significant benefit to most patients.2 A recent review of the risks and benefits of new anticancer agents undergoing Phase 1 testing revealed that 1 out of every 200 patients enrolled died as a

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direct result of taking the drug (the death rate was closer to 1 in every 100 patients during the early part of the study).³ Only a very small percentage of patients (less than 4%) respond at all to these experimental drugs,⁴ and most of the responses are for very short period of time (a matter of weeks only) and involve tumor shrinkage by only a small fraction. Virtually no one is cured of their cancer by treatment with any Phase I agent, and “no data verify that response rates translate into a longer life or better control of symptoms.”⁵ Phase I drugs are thus always experimental but rarely if ever therapeutic.

Poor results such as these have caused some authors to question the ethical basis for Phase I trials.⁶ Despite these grim figures, Phase 1 oncology trials are considered essential to advance cancer drug treatment, and patients often willingly participate, “motivated by hopes for stabilization, improvement, or even cure of their cancer.”⁷ Such active participation despite almost zero chance of cure suggests that patients are either not being given accurate information by their doctors, are willfully ignoring depressing data when they are ill, or are failing to understand the information they are provided.⁸

Assuming legitimate informed consent can be obtained, how can a dying patient go about getting experimental therapy? There are four readily available, common legal mechanisms patients have for access to unapproved drugs: (1) enrollment in a clinical trial sponsored by an institution or pharmaceutical company; (2) obtaining a special or compassionate exemption for treatment from an investigator in a clinical trial; (3) contacting the manufacturer or sponsor directly; and (4) asking the treating physician to file a single patient or emergency IND (investigational new drug) application with FDA.⁹ Each of these four methods differs in the amount of time it takes to obtain an otherwise unavailable drug for treatment of a life-threatening or otherwise untreatable illness, as well as in the number of administrative hurdles patients and their families must overcome. In academic medical centers all four methods are usually available. As a rule sponsors may not charge for unapproved drugs.

Virtually all cancer patients who enroll in clinical trials are receiving drugs which are in either Phase 2 or Phase 3 testing. These drugs may be experimental but at least basic safety and dosing data is available even if no one is certain how well they will work in humans. “Compassionate use” of an experimental drug in the case of serious or life-threatening disease usually is limited to drugs in Phase 2 testing, but there is no rule barring their use while still in Phase I testing. Major cancer centers such as M.D. Anderson may have hundreds of clinical trials actively recruiting patients for treatment

³ Id.
⁴ Id.
⁵ Manish Agrawal and Ezekiel J. Emanuel, Ethics of Phase 1 oncology studies: reexamining the arguments and data, 290 JAMA 1075 (2003).
⁶ Id.
⁷ Id.
⁸ Id.
⁹ Id.
with unapproved, investigational agents\textsuperscript{10} going on at any given time. No data suggest that dying or otherwise untreatable patients have difficulty obtaining Phase 1 drugs quickly\textsuperscript{11} or that such a situation happens frequently. In other words, access to experimental drugs prior to approval is, and has been, an established option for dying or otherwise untreatable patients for years.

\textbf{Why Fight for A “Constitutional Right”?}

If the current system works well and quickly, and patients are not denied access to experimental medications, there would seem to be little need to claim a “right” to Phase I drugs. Nevertheless, the existence of such a “right” was the central claim in Abigail Alliance.\textsuperscript{12} The advantage of having such a right would presumably be that dying patients could simply demand access to a drug without going through any of the administrative hurdles and potential delays involved in the four currently available avenues. Issues which would have been resolved at a later date/time included who would pay for these drugs, and liability issues stemming from a physician’s denial of a “demand” for a drug the doctor thought was either inappropriate for the disease or could not be inadequately consented for. At present, the only individuals in the United States who currently have any constitutional right to healthcare are prisoners in federal prisons,\textsuperscript{13} and even that right is focused on access to basic healthcare, not on access to experimental drugs.

\textit{Abigail Alliance: The Facts and Case History}

This case was first filed\textsuperscript{14} against the United States Food and Drug Administration in 2003 by the Abigail Alliance for Better Access to Developmental Drugs, an advocacy group based in Fredericksburg Virginia. This group was founded by Frank Burroughs, the father of a young woman named Abigail who died at age 21 from head and neck cancer while battling to receive a drug (Iressa) which was not approved at the time of her diagnosis but which ultimately was approved by FDA and later shown to be relatively ineffective in most cancer patients. The suit followed the submission of a sophisticated, joint Citizen’s Petition (CP)\textsuperscript{15} by Abigail Alliance and the Washington Legal Foundation in June 2003 asking FDA to revise its current regulatory approach for allowing dying patients access to experimental drugs and proposing a new, three-tier model for experimental drug regulation. Although the CP claimed that existing mechanisms were inadequate, and that “clinical trials and existing compassionate use programs are

\begin{footnotes}
\item[11] Id.
\item[14] Abigail Alliance for Better Access to Developmental Drugs v. McClellan, Supra.
\item[15] Citizen Petition of the Abigail Alliance and the Washington Legal Foundation to the Food and Drug Administration, U.S. Department of Health and Human Services, In re Tier 1 Initial Approval Program to Expedite the Availability of Lifesaving Drugs, (June 2003).
\end{footnotes}
extremely limited in scale compared to the tens of thousands of patients in need," no empirical data were provided to support this contention.

The Alliance’s initial suit against FDA in federal district court in 2003 sought to enjoin FDA from continuing to enforce a policy which barred the sale of Phase I potentially life-saving investigational drugs to certain mentally competent, terminally ill adult patients. The Alliance advocated that drugs should “be made available as early as the conclusion of the first of three phases of clinical trials.” The wording of this statement notwithstanding, it wasn’t clear if this meant that patients would also have access to drugs which were still undergoing Phase I testing for which the maximum tolerated doses and safety issues were still not known, or only to drugs which had completed Phase 1 testing but which had yet to start Phase 2 testing.

The federal district court dismissed the Alliance’s complaint pursuant to Federal Rule of Civil Procedure 12(b)(6) for failure to state a claim. The Alliance was then joined in court by the Washington Legal Foundation. The plaintiffs advanced multiple arguments in support of their argument that dying or untreatable patients have a constitutional right to unapproved drugs. First, they claimed that denying such drugs amounted to depriving patients of their right of “self-defense”; second, they argued that denial violated a dying patient’s 5th Amendment right to life, liberty or property without adequate due process; and third, they stated that denial of drugs to save one’s life in a situation where the risk-benefit ratio was unique and unnecessary delays could be fatal was in effect a death sentence. No direct right to privacy or “bodily integrity” arguments were raised.

A 3-member panel of the D.C. Circuit Court reversed the federal district court decision by a 2-1 vote, holding that the lower court had erred in dismissing the claim and further noting that (1) the federal government has traditionally not blocked access to new drugs, and (2) holding that the right to access unapproved drugs could be inferred from an individual’s due process right to refuse life-sustaining medical treatments arising out of the Cruzan decision. Viewing the claimed right to potentially life-saving drugs as a fundamental Constitutional right deserving strict scrutiny and accepting the plaintiffs’ 5th Amendment argument, the three-judge panel remanded the case to the district court to determine whether FDA’s policy was “narrowly tailored to serve a compelling [governmental] interest.” The 3-judge decision clearly took the legal and medical communities by surprise.

16 Id.
17 Andrew Pollock, Court Rejects Patient Right to Use Drugs Being Tested, NEW YORK TIMES, August 8, 2007, at A1.
19 Id.
20 Id.
Seemingly displeased with its 3-judge panel decision, the entire D.C. Circuit Court of Appeals re-heard the case en banc, and vacated the judgment, summarily dismissing all of the plaintiffs’ arguments and distinguishing the historical right of access to treatment from the claimed access to unapproved treatments. The plaintiffs filed a Petition for Certiorari with the United States Supreme Court on September 28, 2007. At the time of this writing a decision on the Writ of Certiorari has not been made.

Some Conclusions and a Prediction

The en banc ruling by the D.C. Circuit Court of Appeals that dying patients don’t have a constitutional right for access to unapproved drugs came as no surprise nor was the decision to appeal to the United States Supreme Court. The Supreme Court is no stranger to the issue of whether there is a constitutional right to use of unapproved drugs, and based on prior Supreme Court decisions there is no obvious reason to think that the Court might want to create another non-text-based fundamental right.

In a case almost thirty years ago involving the infamous drug Laetrile (a purported anticancer agent derived from apricot pits) the issue was whether section 505 of the 1938 Federal Food, Drug, and Cosmetic Act (“the Act”) precluded terminally ill cancer patients from obtaining Laetrile, a drug not recognized as “safe and effective” within the meaning of § 201(p) (1) of the Act, 52 Stat. 1041, as amended, 21 U.S.C. § 321 (p)(1). The Court noted that “To accept the proposition that the safety and efficacy standards of the Act have no relevance for terminal patients is to deny the Commissioner’s authority over all drugs, however toxic or ineffectual, for such individuals.” In other words, the importance of the safety and efficacy determination trumped the notion of a “right”. The Court also rightly noted that just because the Act encompassed treatments for terminal diseases did not mean that patients did not already have ways of obtaining access to investigational drugs not yet approved. This is still the case 30 years later. More recently, in Gonzales v. Raich, the Court held that the dispensing of new, unapproved drugs (in this case Cannabis) had to await federal approval, even when their physicians and an individual state (in this case California) approved of their use.

The most recent en banc decision in Abigail Alliance was good news to the medical profession. The American Society of Clinical Oncology noted, “The court made the right decision. Phase I studies are not designed to determine either safety or efficacy, so had this suit prevailed, cancer patients could receive treatments that do not work or are actually harmful. In addition, allowing access to unproved therapies could harm the ability to develop effective new drugs for all cancer patients by deterring participation in clinical trials.” FDA was undoubtedly pleased, since a ruling against FDA would have

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25 Petition for Certiorari, Abigail Alliance, 76 USWL 3189 (September 28. 2007).
27 Id.
28 Gonzales v. Raich, 545 U.S. 1 (2005).
29 Brief for The American Society of Clinical Oncology, The Association of American Medical Colleges, and the National Coalition for Cancer Survivorship at Amici Curiae Supporting Appellees, Abigail
undermined the entire drug approval process. As things now stand, existing government and private programs which provide dying patients access to experimental drugs remain in place, and these remedies remain unaffected by recent federal court decisions.