COMMENT

Cancer, access to investigational drugs, and patient rights in the USA and India

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Around the world, patients and their families, in the face of a cancer diagnosis, wish for and seek out the best, state-of-the-art treatment. In this commentary, the story of one patient in the USA draws attention to what extent demand and expectations for treatment may go, and to the legal decisions and regulatory processes that may intervene to clarify the rights of patients and the protection of patients. In India, in 1999, a set of cancer patients was enrolled in an unauthorised clinical drug trial that, when discovered, raised the question of who–within the rules guiding clinical trial research–was responsible for safeguarding these patients.

While the American case and the Indian case revolve around patients with different types of cancers, and different causes for the attention they generated, nonetheless they illustrate two fundamental concerns in patient care–those of patient protection and of patient rights.

The American case played out in a series of lawsuits filed against the US Food and Drug Administration (FDA). The question raised in these suits is whether access by an adult, terminally ill patient to experimental drugs which have completed Phase 1 clinical trials, but are not yet approved by the FDA, is a fundamental right granted in the US Constitution. Under FDA regulations, "Phase 1 tests are conducted on twenty to eighty subjects and are designed to measure adverse effects associated with increasing doses of a new agent...and if possible, to gain early evidence on effectiveness." (1)

The American case

In 1999, a 19-year-old American woman, Abigail Burroughs, was diagnosed with squamous cell carcinoma of the head and neck, a rare type of cancer for her age group. Abigail underwent standard treatment of chemotherapy and radiation. Nonetheless, she was not cured, and died in 2001. A drug, Erbitux, which had passed Phase 1 clinical trial, became a focus for Abigail, her family, and their supporters as it was believed this would benefit her condition (2). Despite efforts, she did not qualify to enrol in trials of treatments with either genfitinib or cextuximab, but was entered into a trial of erlotinib shortly before her death (3).

During the course of her illness, Abigail told her family that if she survived, she would like them to help cancer patients and other types of patients "where there's an unmet need."(2) Following her death, her father, Frank Burroughs, "realised that the inability of seriously ill patients to obtain effective drugs still under study was a critical unmet need." (2) Therefore, propelled by a desire to honour her wishes to help other patients, her father founded the Abigail Alliance for Better Access to Developmental Drugs in 2001.

With the *pro bono* help of the Washington Legal Foundation, the Abigail Alliance undertook a legal challenge of the FDA, suing the agency on "The contention...that FDA policy violates the Constitutional right to privacy and that the Due Process Clause protects the right of such patients in late stages of disease to decide for themselves whether to assume the risks of unapproved drugs." (4)

Two hearings before the United States Courts for the District of Columbia Circuit were held in 2006; the first hearing did not support the Alliance's arguments, the second hearing did. A majority of judges, dissatisfied with the decision of the panel of three judges who held the second hearing, called for a review by all of the court judges, which was held in March 2007. In August 2007, a ruling was reached against the arguments set forth by the Abigail Alliance (4). A key finding in the ruling stated that "the Alliance ignores one simple fact: It is unlawful to procure experimental drugs not only because they have not been proven effective, but because they have not been proven safe." (4) Finally, in January 2008, the US Supreme Court refused to hear the case (5).

These legal cases, reviewing the question of whether or not an adult has the right to access to drugs not yet approved for use, were identified as challenges to the drug testing, approval, and regulatory procedures of the US Food and Drug Administration (1,3,6).

Health policy experts and ethicists raised concerns about permitting unapproved drug use by patients that may be costly, may place their physicians in potential legal and ethical dilemmas, may subject patients to unproven treatment, may subvert the rationale of clinical trial studies, and may disrupt orderly drug development (1,3,6). While not having the outcomes hoped for by the Abigail Alliance, nonetheless the questions raised in the 2006 court cases by this patient advocate group led the FDA to begin "the process of rewriting its own regulations to make it easier for terminally ill patients not enrolled in clinical trials to have access to investigational drugs." (6) (See also Finkelstein [7]

In the course of these legal challenges, the American Society of Clinical Oncologists (ASCO), a non-profit organisation of 25,000 oncology physicians and health professionals, issued a statement on August 8, 2007, one day after the court ruled that terminally ill patients do not have a right to access to experimental drugs that have not been approved by the FDA. Dr Allen S Lichter, an ASCO officer, stated: "Phase 1 studies are not designed to determine either safety or efficacy, so that cancer patients could receive treatments that do not work or are actually harmful had this suit prevailed. In addition, allowing access to unapproved therapies could harm the nation's ability to develop effective new drugs for all cancer patients by deterring participating in clinical trials." (8)

Prominent journals such as *JAMA, The New England Journal of Medicine,* and the *Hastings Center Report* reviewed the legal cases brought by the Abigail Alliance (1,3,6). Rebecca Dresser, writing in the *Hastings Center Report* prior to the August 2007 decision, identified the attraction of the Abigail Alliance proposal for patients as well as its shortcomings: "Drug testing for safety and effectiveness primarily helps future patients. To advance knowledge, some subjects participating in clinical trials must be assigned to standard therapy...Obtaining early-phase drugs through a physician would be a more attractive option for many people. Thus subject recruitment will be more difficult if the majority's expanded ruling goes into effect." (1)

In 2006, Donald Kennedy, the editor of *Science,* stated that the Abigail Alliance's activities were similar to those of laetrile supporters in the 1970s and 1980s (9). Laetrile, an unproven treatment, had widespread support in the United States, resulting in legislation permitting its use for cancer patients in many states, but ultimately leading in 1979 to a US Supreme Court ruling in favour of the FDA's arguments against the claims for laetrile (6). In the 1970s and 1980s, opposition to various unproven methods of treatment from leading cancer organisations, such as the American Cancer Society and the American Society of Clinical Oncologists, was organised around the principle that the medical establishment knew the medical science, knew the treatments, and knew what was best for their patients suffering from cancer.

Disapproval of "unproven methods of cancer management", a term used to identify those methods unproven by standard scientific research through the clinical trial process, became harder to sustain from the 1980s onwards. In the United States, patients and the lay public asserted their right to know about their disease, their treatments, and to choose what were to become identified as complementary and alternative treatments when either mainstream treatments failed, or were no longer an option based on the patient's stage of disease. In effect, the incorporation of complementary and alternative medicine into the cancer establishment often serves to co-opt patients' arguments for access to non-standardised therapies (10). The arguments raised in the Abigail Alliance case, although about drugs in the development pipeline, have some similarities to discussions raised by proponents of non-standard modalities. Dresser characterises the early court ruling in agreement with the Abigail Alliance, as one "that... embraces popular ideas about the miracles that can occur when terminally-ill patients gain access to novel agents." (1)

In the Abigail Alliance case, the argument stated by the FDA, the mainstream cancer organisations and professional organisations, medical ethicists, researchers, and policy makers is that end-of-life patients, like other patients, should be protected from the unknown effects of an unproven drug. This viewpoint was upheld by the court decision of August 2007, and not reviewed again by the US Supreme Court in 2008, effectively showing agreement.

On the other hand, the Abigail Alliance, serving as patient advocates, evokes sympathy and support for the plight of individual patients suffering from advanced disease, chronic or unusual conditions, in search of effective treatment. The Alliance's arguments pit the perceived uncaring, bureaucratic establishment, represented by emblematic organisations such as the FDA and the National Cancer Institute, against these patients. While their perspective in supporting such patients may be understandable, as Annas argues, patient "choices can and should be limited to reasonable medical alternatives, which themselves are based on evidence. This is...good public policy ."(6)

The Indian case

In 1999 and 2000, at the Regional Cancer Centre (RCC) in Trivandrum, a well-respected Indian Council of Medical Research cancer centre, 25 patients being treated for oral cancer, were given an added treatment, not in the protocol–the chemicals, M4N or G4N. The purpose was "to see if M4N and G4N could be effective cancer drugs in the long run." (11) (See also Nundy and Gulhati [12]) Without the review or approval of the Institutional Review Boards at RCC or at Johns Hopkins University (JHU), Baltimore, USA, a JHU faculty researcher, Ru Chih C Huan, persuaded RCC to engage in the testing of these drugs. The research involved an injection of one of the chemicals "into designated, small portions of the tumour...when the tumour was removed, the effectiveness of the chemical, especially at the injected portions was studied...at the JHU laboratory." (11)

As events unfolded, it became evident that RCC went ahead "with the experiments even though sanction for them, both from the RCC's own ethics committee and from the Drugs Controller General of India came months after the experiments were conducted." (11) As Nundy and Gulhati point out, prior to new regulations promulgated in 2005, under the Indian Drugs and Cosmetics Rules, a lag in conducting phases of clinical trials was to be held between India and the rest of the world. Thus, "if a Phase 3 study had been completed elsewhere, only a Phase 2 study was permitted in India. Even under the new rule, Phase 1 trials will not normally be permitted in India. The old rule was designed to protect Indians from being used as guinea pigs in the testing of unproved drugs of foreign origin..."(12) Thus, the Trivandrum study, which could not be undertaken by the JHU researcher "in the US where legal and ethical formalities left

little leeway in research involving human participants," (11) was presumably in violation of Indian research regulations in place in 1999 and 2000.

In the Trivandrum case, we find patients subjected to an experiment with chemicals "that had successfully tested ...in mice" at JHU (11). Moreover, in the information provided to the patients by RCC "there was no real evidence...to prove that the patients understood...that they were going to be subjected to the first experiments in humans of chemicals...derived from NGDA."(11) It is projected that in the coming years, India will become a centre for clinical trial research. It has a large population "who have not been exposed to many medications but have myriad diseases, ranging from tropical infections to degenerative disorders." (12) In addition, Indian physicians know English, and many hold postgraduate qualifications from the UK and the US; low labour and infrastructure costs help keep research costs down (12).

The failure of the RCC to protect its patients, and of JHU to have adequate control over one of its researchers, provides a cautionary tale. Will the protective legal judgements and regulatory mechanisms that were clarified during the Abigail Alliance's challenges for drug access for terminally ill patients in the USA, be kept in the forefront as India enters the competitive world of drug testing? Nundy and Gulhati urge that Indians enrolled in trials be provided complete information, give voluntary and informed consent, and have access to drugs after they are proven safe, noting that "these things can only be done when the government has strengthened its regulatory system so that it is geared toward guarding the rights of patients and protecting them from exploitation." (12) This exhortation echoes the discussions that emerged in the medical, ethical, and legal debates brought about by the actions of the Abigail Alliance.

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