Should terminally ill patients have the right to take drugs that pass phase I testing?

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YES

Around half a million people will die from cancer related causes in the United States this year. In the US, as in much of the Western world, patients know their diagnosis and are often given a hopeless prognosis. For most, the option of participating in phase I and phase II clinical trials of new drugs that offer some promise helps them remain optimistic. Clearly, they should have the right to take drugs that have passed phase I testing.

The problem is that most cancer patients cannot participate in phase II trials because they are either ineligible or they are unable to fulfil the financial and social requirements for participating in such trials, such as staying in the centres conducting these trials, sometimes for many weeks or months. The problem is clearly not one of safety because these drugs have completed phase I clinical trials and there is sufficient information about them to justify a phase II trial to determine efficacy.

Phase II trials are designed to give the highest probability of a positive outcome. Thus, they have patient eligibility requirements which assure that only the healthiest patients at the earliest point in their disease are entered. These decisions are not based on any reasonable evidence that patients who are ineligible would not benefit, but are strictly designed to fulfil the regulatory requirements established by bodies such as the Federal Drug Administration (FDA) and the regulatory components of industry and academia that govern these clinical trials.[1 2]

Compassionate prescribing

In the modern electronic era, most of the patients with hopeless cancer diagnoses have access through the media and the internet to information about promising new drugs that are in phase II clinical trials. These patients would like very much to receive these drugs to offer them some hope, but for the reasons mentioned above are unable to participate in those trials. So why not offer these drugs to these patients on a compassionate basis?

The first reason given is usually the safety concerns. Without knowledge about how renal function, cardiac function, age, etc affect the action of the phase I drug, side effects might occur that could be harmful to the patient or, perhaps more importantly, the continued development of the drug. I think this objection is relatively minor since it simply states the benefit: risk ratio problem—that is, these patients are prepared to volunteer to expose themselves to increased risk because of their hopeless prognosis and because of the promise of the new drug.

Patients with advanced cancer and limited life expectancy should have the same privilege as all individuals in a free society

The second objection is that it will interfere with the development of the drug. However, in the past, the FDA and the National Cancer Institute have allowed compassionate use of drugs and have found that it actually accelerates development. This is because when patients are offered compassionate use of an experimental drug, their doctors have to collect information as systematically as in the research protocol and submit it to the sponsor. Information is therefore available about use of the drug outside trial conditions. For example, if patients with impaired renal function not only tolerate the drug but respond, it will assist in drug development to have that knowledge collected systematically.

Drug industry profits

Another objection is that the drug industry might use this device to profit from investigation of a phase I drug. I believe this is a trivial objection because the usual strategy for compassionate use is that the drug is provided at cost. The last, and perhaps the most serious, objection is that expanded access would interfere with the clinical trial process. This certainly should not be the case. The clinical trial process is governed by the regulatory bodies in government, in industry, and in academic institutions. The unfortunate consequence of this is that physician scientists, who have the most experience, the most training, the most knowledge, the most productivity, and the most creativity, are completely excluded from this process. Because of the relationship between the regulatory organisations of government, industry, and academia, the academic physician scientist can only implement protocols that have been developed by the drug developer with direction from the regulatory agencies. Expanded access would bring the doctors back into the drug development process and, rather than damage the clinical trial system, would greatly expand its effectiveness and value.

In summary, patients with advanced cancer and limited life expectancy should have the same privilege as all individuals in a free society—that is, to decide their own benefit: risk ratio. It is tragic that regulatory bodies have created a circumstance where people have to live in an aura of hopelessness even though they have the will, the resources, and the ability to expose themselves to the risk of participating in investigational studies and to enjoy the potential for benefit. The solution is legislation or judicial action to permit expanded access to experimental treatments for patients with limited life expectancy.[3 4]

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The United States is considering allowing experimental drugs to be given to people at the end of life. **Emil J Freireich** believes patients should be able to judge the risks for themselves, and **Dean Gesme** counters that the use of such drugs outside trials will damage both individuals and science

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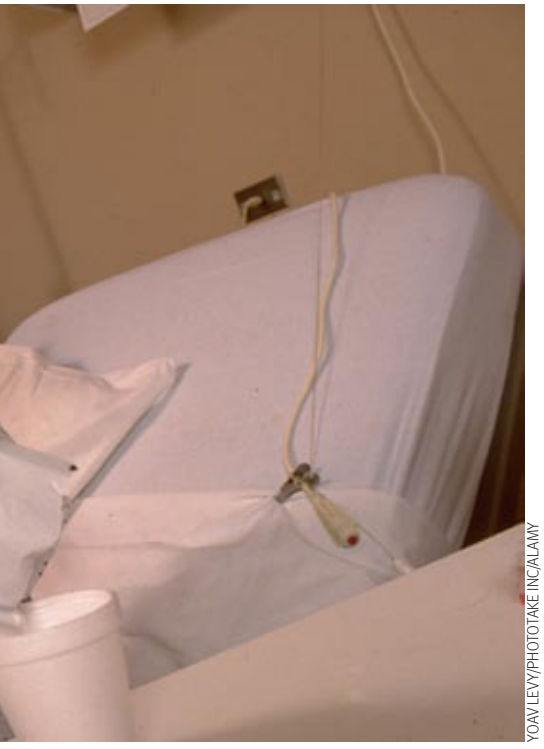
NO Partially tested therapies cannot be allowed to substitute for good medical care. Hippocrates stated that our role as doctors is always to help or, at least, to do no harm. Those precepts apply equally to patients with minor ailments and those with terminal conditions.

In the United States, the Food and Drug Administration has proposed expanded access to investigational drugs for patients with terminal illnesses after initial safety (phase I) trials but before final approval for marketing.[1] This would apply to selected drugs already in phase II and III testing. The legal action filed against the FDA by the Abigail Alliance also seeks to make available drugs for which phase I safety data are known.[2] The US Court of Appeal recently ruled against the alliance, but it is taking the case to the Supreme Court.

The use of drugs after phase I testing and outside clinical trials may still subject patients to toxicities while offering no reasonable expectation of benefit. Phase I trials are intended to evaluate dose safety, while effectiveness of drugs is assessed in phase II and III clinical trials. More than 90% of drugs entering phase I trials are found unacceptable,[3] and, of those approved, most provide incremental improvements rather than lifesaving treatments.



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The allure of promising new drugs continues to engender false hope, which has all too often diverted time, resources, and attention from more appropriate efforts to minimise symptoms and enhance the quality of life for terminally ill patients and their families. Inappropriate expectations for untested new drugs are commonly promulgated by investigators eager for grant funding, companies searching for capital, writers eager for a good storyline, and uncomfortable practitioners who would rather avoid dealing directly with the complexity of end of life issues.

The allure of promising new drugs continues to engender false hope

Damage to clinical trials

Patients may prefer to take partially tested drugs outside trials to avoid the constraints of a larger protocol study. However, this would subvert accrual of patients to phase II and III trials and ultimately delay the approval of those new drugs. Thus the needs of the many may become subservient to the desperate desires of the few.

False hopes for unproved drugs can also erode the clinical trials system by substituting clinical enthusiasm and wishful thinking for evidence based medicine. The best analogy may come from the many years in which autologous bone marrow transplant was considered standard treatment for advanced breast cancer despite the lack of data concerning efficacy. Well designed clinical trials failed to find willing participants as both patients and many doctors were convinced that this procedure was life saving. We now know that thousands of women experienced unnecessary toxicities, prolonged hospital stays, and lost time with families for what has now been shown to be inappropriate care.[4] Rather than repeating this tragedy with each promising new drug, we should focus our clinical energies on the optimal use of existing treatments and the enhancement of the current clinical trials system.

Investigational drugs may not be accessible to patients even if government authorities grant patients the freedom to access them. Most doctors are likely to be unwilling or unable to assume the responsibility of obtaining adequate informed consent from patients who are desperate for treatment and often unable to assimilate the possible risks involved.

Similar issues of liability and oversight may stop institutions from allowing open access to partially tested drugs. The issue of defining who is, or is not, terminally ill[5] can be most difficult, let alone delineating when existing therapies might offer no possible benefit. Indeed, who will decide which of the many investigational drugs would be best for an individual patient? Do we allow the marketplace to substitute for best practices and evidence based medicine?

Many drug firms have opted not to join current expanded access programmes for drugs in later stages of development and are opposed to providing investigational products outside of approved phase II trials.[6] The costs of drug production can be high, with limited production early in a drug's life. More importantly, there is concern that anecdotal toxicities for drugs used outside structured trials might lead to delayed approval, additional expensive testing, or adverse publicity that could jeopardise a process on which costs and profits of millions of dollars are in the balance.

Who will bear the costs of open access to these partially tested drugs? Will government and other payers who are now seeking to minimise payments for marginally beneficial therapies be willing to pay for unproved drugs outside of formal clinical trials?

Finally, while all doctors dream of the miracle cure for each of their terminally ill patients, we must accept the duty and responsibility to conform to both the principles of evidence based medicine and the precepts of appropriate end of life care. This includes the identification of false hopes and the substitution of realistic goals, enlightened hopes, and attainable expectations. This may be the greatest test for the truly caring and compassionate physician.

Competing interests: None declared.

All references are on bmj.com

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