Virtual Mentor

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Clinical Case

Changing the Rules in Times of Crisis: Do Desperate Times Allow Desperate Measures?

Commentary by Mona Loutfy, MD, MPH

Dr Meredith Green hadn't slept in 38 hours. An as-yet-unidentified respiratory virus had overloaded the medicine service at the hospital where she was on staff, and, if the news reports were any indication, there was no end in sight. Preliminary reports suggested the infection could be related to severe acute respiratory syndrome, or SARS, but global medical communication had so far failed to establish anything beyond the fact that the virus was highly contagious, with devastating mortality and morbidity statistics. Roughly 10 percent of those who acquired it would die while another 10 percent would suffer brain damage as a consequence of the raging fevers the disease induced. Neither statistic seemed to be affected by supportive measures, but at the moment nothing else could be done.

Bleary-eyed, Meredith almost didn't see the man waiting for her outside the room of one of her patients. "Dr Green, Dr Green," he said, a note of panic in his voice as he moved away from the wall against which he had been leaning. "Dr Green, I know everyone is doing all they can, but my wife is getting worse. She's delirious now, with that fever you were telling us about."

"I'm so sorry, Mr Patterson," Meredith said as she moved to open the door. "I need to examine her again and work on getting that fever down. We're doing everything we can to stabilize her condition."

"That's just it," Mr Patterson replied as he followed Meredith into the room. "I know how hard you're working, but this is my wife! She's never been sick like this ever. And we have 3 children at home—she just has to get better. I've been doing some reading and something called interferon seemed to help with SARS. Everyone keeps telling me this is like SARS, and even if it's not, interferon is a powerful antiviral medication, isn't it? It could work, couldn't it?"

Meredith stopped and turned back toward the door as she pulled on the gown and gloves of respiratory isolation. "Mr Patterson, I know you want your wife to get better," she said, "but we can't just start treating her with every antiviral in the pharmacy. Interferon is a powerful drug with many potential side effects. No one knows what it might do in a case like this or how it might react with the other medications your wife needs to keep her fever down. We can't start experimenting on patients to find out."

"But why not?" Mr Patterson asked. "Right now she's dying—you warned us about what a fever that high could mean. She's a fighter, my wife, and I know if she could talk to you she would want to try anything, even if it might not work. I know I want you to. If it gives her even a chance it's worth the risk—it can't be worse than dying, can it?"

"But Mr Patterson," Meredith started to say.

"Please, won't you try?" he interrupted. "She's dying! Can't you make an exception when someone is dying?"

Commentary

The situation in which Dr Green finds herself is a difficult one and, surprisingly, not that infrequent. The case highlights the basic principles of biomedical ethics—nonmaleficence, informed consent, benevolence—in a setting faced by health care professionals during the course of an infectious disease outbreak or a life-threatening illness or both. In analyzing this case, I write as the physician who first used interferon in those infected with the severe acute respiratory syndrome virus (SARS) in Toronto. As a specialist and researcher in infectious diseases, I was positioned both ethically and clinically to use an old drug—interferon—in a new disease—SARS—and to investigate the results in the best way possible.

Analyzing the Principles of Medical Ethics

On graduation day, the guiding principle of medicine we swear to uphold is nonmaleficence. As proud new physicians, we take an oath to do no harm. Nonmaleficence applies to the case of Mrs Patterson: her husband is asking the treating physician to use a drug that is experimental, has not been tested for the treatment of Mrs Patterson's disease, has significant side effects, and could worsen her condition. Before any decision is made, each of these factors must be taken into consideration, discussed with Mr Patterson, and explained thoroughly so that he understands them. This case is further complicated by the fact that the patient cannot give her informed consent, thus her husband would be making the decision for her. Could his judgment be clouded by emotions and not reflect his wife's true wishes?

This question leads into a second important principle of medical ethics: informed consent. In its most basic definition, informed consent reflects the right and responsibility of every competent individual to advance his or her welfare. This responsibility is exercised by voluntarily consenting to or refusing recommended medical procedures based on a sufficient knowledge of the benefits, burdens, and risks involved. The ability to give informed consent depends on 4 components: (1) adequate disclosure of information; (2) patient freedom of choice; (3) patient comprehension of information; and (4) patient capacity for decision making. If these 4 requirements are met, then the patient can be said to have made an informed decision. In the current case, the patient cannot give consent or make an informed decision; this task is left to her husband. How can he understand the risks of using interferon when there is no relevant scientific data available for Dr Green to discuss or explain? Can genuinely informed consent truly be obtained in this situation?

The third crucial principle of medical ethics is benevolence. For physicians, this encompasses doing everything in our power to help our patients by preventing death or improving quality of life or both. Under certain circumstances, benevolence can temporarily supersede informed consent; in an emergency situation, for example, it is acceptable to implement procedures such as transfusing blood without consent if a patient's life is in immediate danger. In this case, Mrs Patterson has a life-threatening illness for which there is no accepted therapy. In such an instance, should we not at least try *something,* even if that something is investigational or of little benefit, because the outcome is inevitable and in trying an experimental therapy at least the physicians and family members know that everything possible was tried?

This is a complex question to answer and a difficult decision to make. If the inevitable outcome for the patient without experimental treatment is death, and the experimental drug is one with which we are familiar because of its use in other disease states, it is possible that an experimental application may not harm the patient and might even be of clinical benefit. Such an application is also likely to have psychological benefits for the family. In this situation, some physicians might decide to try using an experimental agent. In practice, it is not uncommon for physicians to use drugs "off-label," that is, to prescribe them for uses not listed on the FDA-approved package insert. As an example, antiretroviral drugs are not labeled for use in postexposure prophylaxis, but we prescribe them to prevent HIV transmission after sexual contact even without experimental data to support this decision. I am neither endorsing nor countering such a decision, but simply pointing out that such use is not unique to Mrs Patterson's case.

The final ethical point that must be considered when evaluating this scenario relates to the challenge of doing research in an outbreak setting or in fatal diseases with low incidence and prevalence. It is very difficult to conduct research in these settings, and many clinicians and researchers suggest that it might be impossible. Yet I believe it is critical to carry out research under these circumstances. We will never answer some of the most difficult and important questions in medicine without doing research on the treatment of rare and potentially fatal diseases. The situation with SARS taught us that we need to be universally prepared to carry out large randomized controlled trials (RCTs) in an outbreak setting to answer questions of how best to treat emerging infectious diseases that may recur or spiral into a pandemic.

The Toronto Experience

During the Toronto SARS outbreak, I utilized interferon treatment in 19 patients, after having reviewed *in vitro* data showing that interferon had the best activity against the SARS-associated virus among a panel of antiviral compounds tested. Together with other researchers in the laboratory and in radiology, I worked to develop an *a priori,* unbiased methodology for examining patient responses to this investigational agent. I would not have tried using interferon without the implementation of such a pilot study.

Furthermore, approval for the use of interferon had to be obtained from Health Canada; this involved speaking with 2 immunologists to get scientific data indicating that it was sound to give interferon in these cases and that doing so would not worsen the disease. In addition, it was necessary to gain approval from the hospital ethics

committee, the pharmacy and therapeutics committee, and the management advisory committee. All of these tasks were carried out in 48 hours, prior to using an experimental drug in patients with a new disease. It is also important to note that, in addition to the regulatory details, I also discussed the risks, benefits, and experimental nature of this treatment with each of my patients. Considerable work and time goes into the use of an experimental drug in a new disease; understandably, in the clinical case depicted here, Mr Patterson might not appreciate or be aware of all these crucial procedures. Even if Dr Green does decide to use an experimental agent to treat Mrs Patterson, she will not do so without considerably more action than a detailed conversation with her patient's husband.

A Case Close to Home

Recently, I have had first-hand experience of this issue from the other side. My mother was diagnosed with amyotrophic lateral sclerosis (ALS), a fatal disease that led to her death a mere 10 months after diagnosis. Earlier in the year she was diagnosed, there was a landmark breakthrough in ALS research, which found that the use of ceftriaxone was effective at reversing the nerve damage in ALS in a mouse model. However, the human clinical trials would not start until the following year and then only in the United States, thereby precluding my mother from a study for possibly the most effective treatment for this horrible progressive disease. Like Mr Patterson, I was faced with the option of asking my mother's specialist to use an experimental drug in a disease where we knew the patient was going to die, regardless of possible intervention on our parts. I asked myself, what is the harm in using an experimental drug in this situation? What if the patient herself were asking for the drug and understood the risks and benefits? Should we preclude such a patient from trying an experimental drug when all other treatment options have been exhausted? Interferon and ceftriaxone are drugs we use quite often in clinical practice, so we know their side effects extremely well. Can I transfer that knowledge to another disease state and use these drugs off-label when they have not been thoroughly investigated for this disease state?

Conclusions

Although Mrs Patterson's case presents many challenges, it is one that most physicians are likely to face at some point during their careers. Thorough consideration of the guiding principles of nonmaleficence, informed consent, benevolence, and the ethics of sound research can help guide the ultimate decision of whether or not to use an experimental therapy under dire circumstances. In my view, experimental treatment should always be used in a research setting, not as a haphazard clinical guess. An "n-of-1" for the use of an experimental drug is of no benefit to the patient, the family, others suffering from the disease, or the community at large. If, for example, a patient's condition improves after an experimental drug was given, do we attribute this improvement to the drug or to the natural history of the disease? Without a carefully designed research study—even a pilot study designed on very short notice—such a question can never be answered. The results of this "n-of-1" case can give false hope to other patients and their families who may then attempt a desperate search for an unproven treatment. If an experimental drug is not used in a research setting, any clinical results are of no benefit to other individuals with the same disease or to society as a whole.

In the case of Mr and Mrs Patterson, the most useful course of action for Dr Green is to investigate the effects of interferon for the treatment of the emerging respiratory virus, possibly in a pilot study or in a similar scientific matter. However, the gold standard of assessing the ultimate efficacy of a drug is through a RCT. Every effort should be made to carry out such a trial, even in diseases that occur either in outbreaks or that are life-threatening with a low incidence and prevalence rate. The benefits of such research are incalculable.

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