ETHICAL IMPLICATIONS OF MARKETING A LETHAL DRUG

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BACKGROUND

I'm a protein engineer working at Ariad Pharmaceuticals, a company that specializes in treating different types of cancers in humans. I, with the assistance of millions of Foldit players, have recently made a breakthrough in solving the folding pattern of the mutated form of the V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) protein's active, or binding site. Normally, the KRAS protein, which comes from the KRAS gene, binds to Guanosine Triphosphate and actives a signal transduction pathway which allows a cell to reproduce [1]. However, this mutated form binds to the same substrate, GTP, but without restriction, allowing the host cell to divide uncontrollably and form tumors, most commonly in the lungs [2]. Due to my aforementioned breakthrough, I was able to develop an explanation for the mutated protein's binding pattern with Guanosine Triphosphate (GTP), which allowed me to develop an inhibitor that can stop the mutated KRAS protein by blocking its active site, thus significantly slowing the rate of reproduction of cancerous lung cells and allowing for an extended window of treatment for an affected patient. With the newfound information, 253 different inhibitor models were created, each based on different possible configurations of the mutated KRAS' active site. Each model was tested in vitro by splicing into a normal lung cell's DNA the mutated KRAS gene using restriction endonucleases, which are enzymes that cleave DNA sequences, and a plasmid containing said mutated KRAS gene. Using Zinc Fingers, the plasmid was then integrated into the cell's DNA [3]. The inhibitor is then injected into the cell and the cell's growth rate was monitored. Eight inhibitor models were shown to be effective (that is, the rate of cell growth decreased by a factor of at least 2) in blocking the mutated KRAS' active site in all ten trials for each inhibitor.

These eight inhibitors were then ran through a similar test as the previous one, except the cells contain the normal, non-mutated version of the KRAS gene. This test is to see if the growth-limiting property of the inhibitors only affects oncolytic lung cells and not normal lung cells, as that would be lethal since we need to continually replace our lung cells at a steady rate. Four inhibitors were shown to leave a normal, healthy cell unaffected.

The next test was to show which inhibitors were non-lethal in a living system, and thus were tested on laboratory mice in vivo. Forty mice were grown containing the mutated KRAS gene using Dr. Capecchi's method for creating transgenic mice [4]. The mice were then split into 4 groups of 10, and each group was assigned an inhibitor. Each mouse ingested a pill containing a concentration of one of the inhibitors. The mice's vitals were then monitored, and if an inhibitor was shown to have adverse effects, such as fluctuations of homeostatic temperature, dehydration, etc. then the inhibitor was deemed a failure. Only two inhibitors passed this test, and were ready to be tested on humans.

250 test subjects, each one a volunteer from a network of hospitals in Rhode Island, were confirmed to have the mutated KRAS gene and were in Stage IIIB of non-small cell lung cancer, which means their chances of survival through normal lung cancer treatment was about ten percent [5]. These subjects were given weekly supplements of one of the inhibitors (which will now be referred to as Inhibitor A and Inhibitor B) for a year. Of the 125 subjects that took weekly supplements of Inhibitor A, 95, or 76 percent, were shown to have been completely cured of lung cancer, while of the 125 subjects that ingested inhibitor B, 75, or 60 percent, were shown to have been completely cured of lung cancer. I concluded that Inhibitor A was more effective than Inhibitor B at blocking the mutated KRAS' active site, and thus a more effective treatment to Stage IIIB of non-small cell lung cancer than any other method in practice due solely to the significantly higher survival rate of users of Inhibitor A as opposed to Inhibitor B and no inhibitor use. Ariad decides to name my inhibitor "Nicent" because it cured **NI**nety five, or 76 per**CENT** of the individuals it was tested on. Nicent is then marketed and released in North America to much praise.

SITUATION

Two months after being released, Nicent is discovered to cause individuals with a mutation in their anaplastic lymphoma kinase (ALK) gene to die within an hour of ingesting the inhibitor due to the proteins the ALK gene codes for forming a toxic byproduct when interacting with Nicent [6]. This mutated ALK gene is only found in about ten percent of humans and is homogenous throughout the North America. The ALK gene mutation does not affect any rate of lung cancer development in humans. Oncologists aren't able to test for the presence of the mutated ALK gene during chemotherapy, as the test takes a month to complete and oncologists do not want to put the patient at risk for metastasis, or when the cancer reaches other parts of the body, because the survival rate drops to below ten percent and neither inhibitor can save the patient at that point [4]. Additionally, the tests are very expensive, costing upwards of $4,000, and would most likely leave most patients in a position of financial instability [7].

About every 4 weeks, a report is filed citing the cause of death during chemotherapy to be Nicent's interaction with the ALK gene. However, every three days, Nicent is cited as a component to a patient's recovery from lung cancer.

Inhibitor B's interaction with the mutated ALK gene was soon tested and was determined to be non-lethal to individuals with said gene.

QUESTIONS

This scenario raises a series of ethical question, including is one section of a public more important than another, if further research should be done on Nicent to improve it, or is it not worth the effort, how will I be effected if I choose not to recall he product versus if I do choose to recall it, whether to recall Nicent and replace it with the much less effective but non-lethal Inhibitor B, or continue producing Nicent due to its high rate of success or seek out an alternative choice. From my research, given the specific nature of this situation, My research and development process was, according to Pam McGrath in *Ethical Issues in the 21st Century*, completely ethical and justified, thus removing that factor from consideration [8]. I was unable useful articles directly pertaining to these questions. However, a case study by Stanford's Biodesign department provided me with different ways of framing this situation [9].

BY THE NUMBERS – LIVES LOST VERSUS LIVES SAVED

As stated above, patients with Stage IIIB non-small lung cancer displayed a survival rate of about ten percent without aid from either Inhibitor A or Inhibitor B. With aid from Inhibitor A, 76 percent of individuals survived, while with aid from Inhibitor B, 60 percent of individuals survived. However, Nicent immediately terminates 10 percent of individuals with Stage IIIB non-small lung cancer, essentially lowering its effectiveness to 66 percent. Speaking strictly in terms of lives saved versus lives lost, I would be saving six additional lives for every one hundred people treated if I continue using Nicent as opposed to Inhibitor B. However, many people that would have otherwise survived the standard chemotherapy treatment, or treatment from Inhibitor B, would be killed by the drug.

According to the Biomedical Engineering Society (BMES) Code of Ethics, I must "use [my] knowledge, skills, and abilities to enhance the safety, health, and welfare of the public" [10]. By creating a net increase in lives saved, I am promoting the health, safety, and welfare of the general public. Under this particular section, continuing to market Nicent would be the ethical option, since more individuals would benefit from the drug than would be hurt. However, this is a strictly numbers based conclusion, and human beings should not be limited to digits [11].

Parts of a Public

As mentioned above, two relevant groups exist in this case: those without the mutated ALK gene, and those with the normal ALK gene. Although the former group is much larger than the latter, does that mean it takes precedent before the smaller group?

Assuming both groups are equal despite their disparity in size, the more ethical option shifts to recalling Nicent and releasing Inhibitor B in its place, as harming one group for another's benefit could be considered dishonorable, and thereby be in violation of of the BMES Code of Ethics [10] . In the former case, the mutated ALK gene group was harmed while the normal ALK gene group benefitted; in this case, both groups benefit, albeit the normal ALK gene group is benefitted to a lesser extent than in the former case.

IN RESPECT TO INTEGRITY

Due to NSPE's Code of Ethics for Engineers, as well as the journalistic work of various reporters, Nicent's interaction with the mutated ALK gene is well known publically. As of now, Ariad is being criticized for marketing a drug that can be lethal in specific cases and cancer centers are being criticized for utilizing the drug and killing patients unknowingly [12]. According to the BMES Code of Ethics, I am required to "consider the larger consequences of [my] work in regard to […] delivery of health care" [10]. By continuing to market this drug, I am hurting the integrity of myself, my company, my profession, and of the cancer centers that use my drug. Under various sections of NSPE's Code of Ethics for Engineers, including the preamble, I must hold, at the very least, the integrity of my profession to a high standard [11]. Therefore, in order to preserve the reputation and integrity of the above mentioned entities, I should recall Nicent.

FINANCIAL IMPLICATIONS

The long-term cost of recalling all of Nicent is tough to predict, but, combining information from various accounts of product recall and an analysis from my lawyer brother, is probably between 50 million and a billion dollars [12][13][14]. Calculated from stock market share price and number of shares outstanding, Ariad is worth around 1.29 billion dollars [15][16][17]. This deficit would significantly damage Ariad's research funding for its projects, including various other lung cancer drugs, and could even put Ariad out of business [18]. If Ariad goes out of business, 295 people will lose their jobs because of the mistake I made [19]. According to NSPE's Code of Ethics for Engineers, I cannot "injure […] directly or indirectly […] the employment of other engineers" [11]. By recalling the drug, I will be breaking this code. If I continue to market Nicent, I would be breaking a different section of NSPE's Code of Ethics for Engineers, which states that I shall "hold paramount the safety, health, and welfare of the public" [11]. By my own conclusion above in the section titled "Parts of a Public", recalling Nicent would be the more ethical option to

pursue in terms of holding paramount the safety, health, and welfare of the public; by continuing to market Nicent, I would be placing the employment of other engineers above the safety, health, and welfare of the general public.

FUTURE DEVELOPMENTAL FACTORS

Information about the allele frequency or the distribution within a population, of the mutated ALK gene is sparse. Our current understanding is that the ALK gene is found homogeneously throughout the world, but the frequency of the mutated variant depends largely on the environment a person is situated in; someone who experiences a larger amount of carcinogens per day is much more subject to developing the mutation [20]. As a result of this, a limited recall of Nicent would not be practical, as these communities are not centralized in a location and are instead scattered throughout North America.

Nicent could theoretically be modified to account for the mutated ALK gene, and thus, after a few additional years of research, be re-released. However, if recalling the product ends up killing the company that manufactured it, then a re-release of an improved Nicent may never arise. Additionally, Ariad's pipeline shows promising future drugs that could combat or cure other cancers, such as supplements for gastrointestinal stromal tumors and treatments for biliary cancer [19]. By proceeding with an action that could terminate these drugs from reaching the market, I will be violating NSPE's Code of Ethics for Engineers by failing to serve the public interest [11].

MARKETING BOTH NICENT AND INHIBITOR B SIMULTANIOUSLY

Both recalling and continuing to market Nicent have been shown to violate various ethical codes found within NSPE's and the BMES Code of Ethics. However, an alternative solution exists that does not appear to break any listed codes: marketing both Nicent and Inhibitor B at the same time.

Rebranding Nicent as a lung cancer treatment alternative for people who happen to know they contain the normal variant of the ALK gene would eliminate the need to recall that product, thus no longer putting the jobs of my fellow engineers at risk. By simultaneously marketing Inhibitor B at the same time as Nicent, I would also no longer be dishonoring my profession, thus no longer in violation of that code in the BMES Code of Ethics. Additionally, by marketing Nicent as purely an alternative to Inhibitor B based upon the discretion of the oncologist prescribing the drug, I would no longer be in violation of harming the integrity of any party involved, thus no longer infringing upon the preamble of the NSPE's Code of Ethics for Engineers [10].

AN ETHICAL OPTION

Under the assumption that staying within the bounds of both the BMES Code of Ethics and the NSPE's Code of Ethics for Engineers deems an action ethical, then the choice I will be making for the scenario presented is to market both Nicent and Inhibitor B, as it has been shown to be the option to present the least amount of ethical issues. If I were to recall Nicent, I would intentionally be putting in jeopardy the jobs of my fellow engineers. If I were to continue marketing just Nicent, I would be harming the reputation of many of the entities involved in the distribution and administration of the drug. This option also leaves open the opportunity for Ariad to distribute potentially life-saving drugs in the future, thus serving the best interest of the public. Additionally, I consulted my mother, who struggled with colon cancer for a few years, asking if she would use Nicent if it applied to colon cancer instead of lung cancer. She made it clear that, even though the odds of her surviving when ingesting the drug were in her favor, she would not want any risk involved when using chemotherapy supplements [21].

In order to avoid this scenario altogether, a limited release of the product should be utilized. If there is a major issue with the product, recalling it from a small area, instead of the entirety of North America, would be much less devastating to the parent company. In addition, if technology advances to the point where genetic tests are as quick and easy as blood tests, then this would eliminate any issues regarding gene mutation interactions with a product.

In future ethical scenarios similar to this, generally, if a choice leads to a certain group of people being targeted or treated unfairly, that choice is usually the absolute last resort.

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