

Helping Cancer Patients Take Their Medicine

One of the cruel ironies of cancer is that, in order to be cured, you often have to eat poison. That's because the drugs that kill cancer cells can also kill you. It all depends on the dosage. In dosages considered to be therapeutic, the drug obviously does not kill — but it can make you feel extremely ill, nauseous, and possibly regurgitate the ingested dose. Not only does vomiting make you feel awful, it lowers the amount of the drug in the blood stream, and makes treatment more difficult to administer because of the variable dose the patient receives. And that can lower your chances of receiving effective therapy.

When patients are in the hospital for treatment, they have enough on their minds without worrying about getting sick from the treatment that is supposed to make them well. That's why a clinical study is now underway at Johns Hopkins Oncology Center (JHOC). The purpose of the study is to determine if a new method for delivering a cytotoxic drug is safe and effective — one that allows such drugs to be administered intravenously rather than orally, with far fewer side effects and much greater patient comfort. The breakthrough behind this new approach is the mixing technology embodied in the Microfluidizer® processor. Because of this technology, the drugs can be mixed with compounds that allow the drugs to circulate in the blood and more directly target the appropriate tissues with the goal of being more effective.

The drug being tested in a U.S. FDA approved Phase I Clinical Trial is called *Spartaject*™ Busulfan for Injectable Suspension— an injectable form of busulfan. Busulfan is a cytotoxic drug that has been approved for years to treat patients with a certain form of leukemia, and has been used “off label” to treat other diseases where the patient may require a bone marrow transplant. Busulfan's job is to kill the patient's own bone marrow cells so they can be replaced with healthy cells from a donor. Sparta Pharmaceuticals is the name of the Horsham (Pa.) company that is developing this new form of the drug and Chris Phillips is the company's Director of Manufacturing.

“Busulfan is very toxic,” says Phillips. “What it does is irreversibly bind to DNA and other cellular complexes and essentially stops the normal metabolic machinery from working. It kills cells. Bone marrow cells are more susceptible to cytotoxic agents than other normal cells because they are rapidly growing and are continuously being replenished. For that reason, busulfan has been found to be very useful in patients who require a bone marrow transplant because it can effectively wipe out their cancerous bone marrow, making it possible for them to receive a donation of healthy cells.”

“The problem”, says Phillips, “is that busulfan is virtually insoluble in water. That means it can't be administered as an IV solution without potentially irritating additives and solubilizing agents and instead must presently be taken orally. When a person ingests it,” says Phillips, “it has to migrate across the stomach lining, intestinal tract, and through the blood system before it can get to the target tissue. During oral dosing, busulfan has to traverse all of these different tissues, where it evokes its cytotoxic activity on the transient non-target tissues, leading to a number of unwanted side effects and can make you feel weak, nauseous and can effect the lungs, skin and liver.”

A typical busulfan dosage for a bone marrow transplant could be 30 2-milligram tablets, taken four times a day for four days — but may vary because each patient may absorb the drug differently. “It's very important to closely monitor the plasma levels so that the patient is not under or overdosed. To dose the patient, you have to give them some, then monitor how much you have in the blood stream. It's different in different patients.”



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Children Particularly Vulnerable

Treating children with cancer is particularly difficult, according to Phillips. “Busulfan is used in pediatric cases because it’s a substitute for whole-body irradiation. Children are much more rapidly growing than adults, so their bodies are more sensitive to the negative side effects of irradiation — possibly damaging nerves, the brain and stunting growth. Additionally, when a child takes busulfan, it is more difficult to monitor because of their lower body weight and great care must be exercised to minimize side-effects.”

Sparta’s approach is to bypass the intestinal tract altogether and go directly into the bloodstream — and then straight to the bone marrow. “Our approach is much more target specific”, he says, “because we prepare the microscopic drug particles of busulfan in a lipid monolayer that enter directly into the bloodstream, dissolve, and pass into the bone marrow, as opposed to interacting with every cell with which the drug would otherwise come into contact.”

There has been a demand to replace the oral dosing regimen for years. The problem has been how to mix the insoluble drug in a carrier solution without the use of potentially irritating additives and solubilizing agents and then how to “mask” the drug in an agent that would stabilize the drug and be more easily tolerated by the patient.

The answer was to use Microfluidizer processor technology. This is a device which can combine otherwise “uncombinable” compounds in suspensions (particles in a liquid) or emulsions (droplets in liquids). In this case, the machine is used to create an emulsion busulfan with a mixture of lipids in an aqueous buffer. The lipids form a monolayer around the microscopic drug particles which enables them able to form a stable suspension and then be administered intravenously to the patient in a safe and well tolerated way.

Phillips says that the clinical trial now underway has been positive and is expected to run through the end of 1997. The Microfluidizer processor, he says, “creates a preparation that has excellent consistency and reproducibility. The equipment was directly scalable from small development batches right on through to clinical scale manufacturing and we are able to manufacture this product under cGMPs (current Good Manufacturing Practices). The Microfluidizer processor was the equipment that was instrumental in pulling all of our formulation components and the active pharmaceutical ingredient together,” Phillips says. “It is the flexibility throughout development, ease of scalability, speed of use and the ability to tightly control critical process parameters that makes this equipment a key technology in developing this drug delivery system and makes this potential new form of cancer therapy possible.”



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