Iodized Cancer Therapy

Iodine may be the key to making some incurable cancers more susceptible to radiation therapy

By JANET RALOFF

Several experimental cancer-treatment strategies are tapping iodine's ability to enhance the cell-killing potency of ionizing radiation. By selectively incorporating iodine into the DNA of cancer cells, researchers can now make tumors more sensitive to radiation therapy than surrounding, healthy tissue. This suggests it may be possible to mitigate some of the toxic side effects now experienced by patients undergoing conventional radiation therapy. Even more exciting, some researchers believe, is the promise these methods hold for treating – perhaps destroying – several currently incurable cancers.

At the National Cancer Institute in Bethesda, Md., radiation therapist Timothy Kinsella has been irradiating patients with advanced, high-grade (generally incurable) glioblastoma brain tumors or other metastasized tumors. Prior to irradiation, the patients receive intravenous doses of the iodine-based drug, iododeoxyuridine (IdUrd).

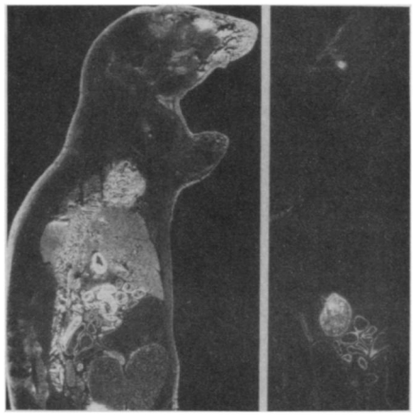
IdUrd is an analog of the DNA nucleoside thymidine – one of the four chemical bases, or building blocks, used to code genetic information into DNA. As IdUrd circulates through the body, cells that are dividing – and therefore synthesizing DNA – tend to incorporate some of the IdUrd into their DNA in place of thymidine. How much a rapidly growing tissue incorporates tends to increase as blood levels of the drug increase. Since tumor cells are among the most rapidly proliferating, they incorporate a proportionately large share of any IdUrd circulating in the blood. In fact, research shows that the drug almost exclusively settles in cells of the tumor, bone marrow, skin and gut.

The drug can be toxic at high doses, reducing or even shutting off the bone marrow's production of blood platelets and irritating mucosal cells in the mouth and epithelial cells in the skin. However, Kinsella and his colleagues at the National Institutes of Health (NIH) have been able to incorporate IdUrd in as many as 50 to 70 percent of the cells of some tumors without causing unmanageable toxicity.

In the November 1985 INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY AND PHYSICS, Kinsella and his colleagues report on radiation treatment of 24 patients with virulent and radiation-resistant incurable cancers. Intravenous pretreatment with IdUrd appeared to slow or halt the progression of cancer in at least 13, including 6 of 10 patients with glioblastoma multiforme.

What causes IdUrd to increase a cell's susceptibility to radiation is still unknown, Kinsella says, though he suspects it may have something to do with the chemical formation of cell-toxic free radicals – short-lived and highly reactive molecular fragments having one or more unpaired electrons. But if the mechanism is undemonstrated, the enhanced radiation sensitivity is not: His studies with cells in culture indicate one can get a doubling in the cell-killing effectiveness of X-rays following IdUrd treatment.

Now Kinsella is trying to improve incorporation of IdUrd into the body without increasing a patient's dose by supplementing the treatment, using a drug that blocks endogenous thymidine production. Although he's demonstrated the principle in tissue-culture tests, it has yet to be proven in either animals or humans. "Those are the studies that we're going to concentrate on over the next few months," Kinsella says.



Irwin Fand, SUNY at Stony Brook

Cross section of rat treated with radioactively tagged IdUrd. Bright areas in the left radiograph show distribution of iodine compound immediately after treatment. Right photo of similar animal, 48 hours after treatment, indicates IdUrd settled mainly in its brain tumor (bright spot in top of photo) and gut.

At Brookhaven National Laboratory in Upton, N.Y., physicist Ralph Fairchild is taking this work a step further. Not only does iodine enhance the sensitivity of cells to radiation, but, he points out, when irradiated with X-rays of the proper energy, iodine will also become "activated," unleashing a cascade of biologically toxic electrons (see diagram). Called an Auger (pronounced *o-zhay)* cascade, these electrons should further enhance the potency of radiation therapy, he explains. The treatment, however, is already sparking controversy. Some, like Kinsella, believe its theoretical advantages promise more than it will actually deliver.

For this "photon-activation" (X-rays are a type of photon) therapy to work, Fairchild explains, the tumor's DNA-bound iodine must be irradiated with the low-energy X-rays capable of knocking out one of the iodine's low-orbiting electrons. When a knockout occurs, another of the iodine's electrons will cascade down from a higher orbital to fill the hole. This sets into motion a chain of cascading electrons, each trying to fill the hole created by the movement of the last. As each electron cascades down, it emits a characteristic X-ray which itself might knock out an electron, further perpetuating the cascade.

"It's the electron shower [rather than the accompanying characteristic X-rays] that makes the cascade so toxic," Fairchild says. In terms of their "relative biological effectiveness" – or toxicity – the electron cascade is at least as damaging as X-rays, sometimes considerably more so, depending on the number of electrons in the cascade. But unlike X-rays, which can travel great distances through tissue, shedding cell-killing energy all along the way, the cascade's electrons deposit their toxic energy quite close to their source. For cells containing IdUrd, the cascade's electrons deposit their energy "all within about three base pairs on the DNA strand," Fairchild says. And that suggests that the cascade-initiated radiation damage should be quite "clean" – that is, it should kill what it is supposed to, the cancer cells, and not neighboring tissue (provided that the neighboring tissue is not synthesizing DNA).

To further limit the therapy's damage to

healthy tissue, the cancer treatment would not use an external source of X-rays to irradiate the tumor. Instead, a needle-sized capsule, or "seed," of radioactive samarium-145 would be surgically implanted directly into the tumor for about five days.

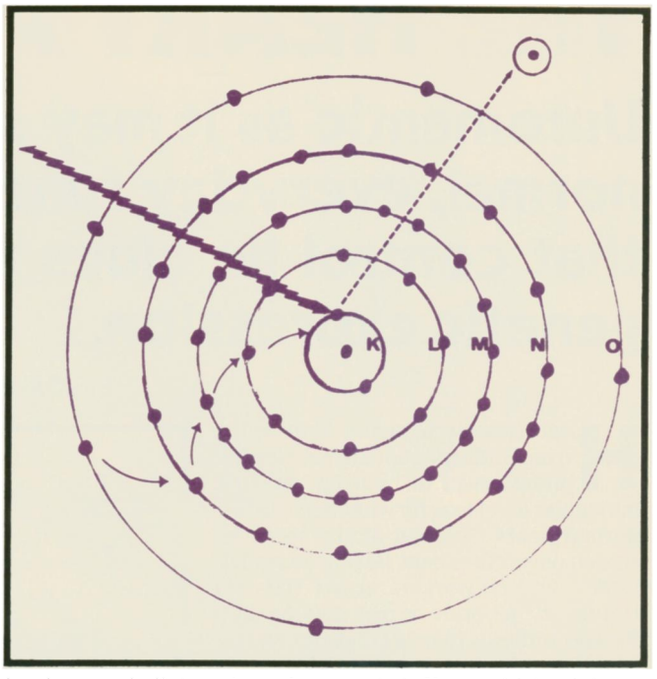
The idea of harnessing Auger cascades for cancer treatment has been around for a long time, Fairchild says. Attention initially focused on radioactive iodine-125 as the cascade source, but that can damage any other rapidly growing tissue. So Fairchild has instead elected to use non-radioactive iodine-127 as the radiation-sensitizing agent and electron-cascade source.

To stimulate a cascade in this stable element, he has to "activate" it with the appropriate low-energy X-rays. While its Auger cascade produces only half as many electrons as the radioactive iodine-125, this stable isotope eliminates the risk of subjecting any other IdUrd repositories to electron-cascade or enhanced-radiation damage.

The Brookhaven group's preliminary investigations of photon-activation therapy's potential have so far demonstrated that mice with a cancer known as Harding-Passey melanoma will accumulate intravenously administered IdUrd into the tumor's DNA at levels that in humans might prove therapeutic. In recently completed studies, the researchers have also demonstrated the iodine-127 Auger-cascade effect in cultured cells that had been allowed to incorporate IdUrd. According to biologist Brenda Laster, who headed the study, "We saw a significant dose enhancement — an enhancement that approached 50 percent" — in cell damage just attributable to the iodine-127 Auger cascades. The next step, she says, is to irradiate IdUrd-sensitized tumor cells in mice to verify that the same measure of enhancement occurs in the living animal.

Kinsella recently completed a tissue-culture study investigating the cell-killing potency of this photon-activation therapy. In it, he compared traditional high-energy radiotherapy of IdUrd-pretreated cells with photon activation's low-energy radiotherapy using an external X-ray source (not the implant). "And we saw no cascade effect," Kinsella told SCIENCE NEWS. He says the study showed that "you get [dose] enhancement with external radiation, but there doesn't appear to be any difference between using a 40 kilo-electron-volt (keV) photon and a 2-4 million-electron-volt (MeV) X-ray." As a result, he is now highly skeptical about the added value of photon-activation therapy's electron-cascade action.

However, Laster points out, "He [Kinsella] doesn't have available to him a monochromatic source" — an X-ray source emitting photons all having the same low energy needed to activate iodine. As a result, she says, it's possible that Kinsella didn't have enough photons of the right energy to even test for a cascade effect. In any case, she says, he hasn't proven that the Auger cascade didn't occur nor that it didn't play a substantial role in enhancing the radiation dose effect.



Electrons orbit the iodine nucleus in a series of "shells." The innermost K-shell contains 2 electrons, the next L-shell contains 8, the M-shell 18, the N-shell 18 and the O-shell 7. When iodine is irradiated with low-energy X-rays, there's a high likelihood that a K-shell electron will be knocked out. That would prompt an L-shell electron to drop down, filling that hole but creating an L-shell hole. An M-shell electron would then drop down to fill the L-shell hole . . . and so on. Each time an electron cascades down a shell, it emits a characteristic X-ray, which might itself knock out an electron, perpetuating the cascade.

She says her group at Brookhaven had to use the Cornell High Energy Synchrotron Source (CHESS) facility in Ithaca, N.Y., in order to get the flux of nothing-but-34-keV X-rays that ultimately demonstrated iodine activation in their most recent tests. Short of having access to the CHESS facility — which can be tuned to deliver 99.9 percent of its photons at a prescribed energy — one has to use the natural decay output of a source like samarium to attain the precise low-energy (30 to 60 keV) X-rays necessary for iodine's activation, explains Brookhaven physicist William Thomlinson, who directed the photon-beam use in these studies. At present, samarium-145 radioisotope sources are not commerically available, so Fairchild's group is creating its own from samarium-144.

But even if the number of IdUrd-treated cells that die is the same at irradiation with 40 keV and 3 MeV photons, as Kinsella's study suggests, that doesn't mean the therapies would necessarily have a comparable effect on a patient. The reason, Thomlinson explains, is that if some 40 percent of the overall dose enhancement seen with 40 keV irradiation is due to electron-cascade effects — as the Brookhaven data would suggest — then more of the cell deaths would have resulted from "clean kills," energy targeted quite selectively on the iodine-treated tumor cells. By contrast, high-energy X-rays would deliver proportionately more of their cell-killing energy outside of the target area — in adjacent healthy tissue.

Among those who share Fairchild and Laster's optimism over photon-activation therapy's potential is Reinhard Gahbauer, chief of radiation oncology at Ohio State University Hospital in Columbus. Although this therapy "is investigational — not clinically proven," he told SCIENCE NEWS, "we are keenly interested in it." So much so, in fact, that he began clinical trials of the treatment in January.

So that the IdUrd differential between tumor and normal tissue is maximized, the best test of photon-activation therapy requires a tumor growing within tissue — like the brain — that is not rapidly dividing. Initially, one would also like to test it in cases where participation in the trial therapy won't require the patient to forgo lifesaving treatment. And that explains why Gahbauer's clinical trials will focus on 20 or 25 patients with glioblastoma multiforme; this brain tumor, which he notes currently accounts for about 2 percent of all cancer deaths in the United States, usually brings death within six months of diagnosis.

Gahbauer cautions that his group is probably several years away from knowing how successful — if at all — the new strategy will prove in halting the ravages of this cancer. But Kinsella's work certainly suggests that the prognosis for some previously intractable cancers may brighten as a result of his and other experimental attempts to enhance radiotherapy's potency with iodine. □