

International Study of Hyperthermia Spurs Hope in U.S. Advocates

By Renee Twombly

Successful use of targeted heat therapy with chemotherapy in treatment of soft-tissue sarcoma has given U.S. advocates of local hyperthermia new hope that the treatment they so believe in will now be taken seriously.

The phase III study, reported in September at the European Society of Medical Oncology meeting in Berlin, included 341 patients at multiple centers in Europe and at one in the United States. It showed that patients with soft-tissue sarcomas at high risk of spreading, randomized to receive hyperthermia in addition to chemotherapy, had a median disease-free survival time of 32 months. Patients randomized to chemotherapy alone had a median disease-free survival of 18 months. The difference was statistically significant. However, overall survival showed no statistically significant difference. The most frequent side effect of the heat therapy (40–43 °C or 104–109 °F) was mild to moderate discomfort, reported in 45% of patients, and the most serious toxic effect was severe burns, seen in one patient (0.6%). Blisters occurred in 17.8%.

The study's lead investigator, Rolf Issels, M.D., Ph.D., said the findings "provide a new standard treatment option, and we believe they are likely to change the way many specialists treat these tumors.

"But the implications of these findings are more far-reaching," added Issels, a professor of medical oncology at Klinikum Grosshadern Medical Center at the University of Munich. "This is also the first clear evidence that targeted heat therapy adds to chemotherapy. We expect our findings will encourage other researchers to test the approach in other locally advanced cancers."

In the United States, longtime champions of hyperthermia echoed that enthusiasm. "We are on a verge, I think, of a major new adjuvant cancer therapy that will not replace chemotherapy or radiation but will make them work a lot better," said Elizabeth A. Repasky, Ph.D., of Roswell Park Cancer Institute, Buffalo, N.Y., and president of the Society for Thermal Medicine, which promotes basic research and clinical application of hyperthermia.

Others, however, are frustrated that advances already documented have not led to a new look at hyperthermia in U.S. cancer clinics. "I have been in the field 20 years, and I see how much benefit patients have, but institutions are not willing to use it," said Zeljko Vujaskovic, M.D., Ph.D., a radiation oncologist at Duke University Medical Center. Duke has long led research into hyperthermia and is the only U.S. institution that participated in the Issels study.

The reasons for that reluctance include the technical demands needed to operate the machinery, the current necessity of inserting probes into tumors to accurately measure temperature, and the historically low insurance reimbursement rates.

The lack of abundant evidence that the treatment could affect overall survival may also play a role. In a point-counterpoint debate on controversies in medical physics, published by the American Association of Physicists in Medicine in 2008, Peter Corry, Ph.D., of the University of Arkansas for Medical Sciences, pointed out that "there are no reports of its application to the treatment of potentially curable cancers where a significant impact might be possible. Even in the cases where some benefit was claimed, it was often marginal."

Despite these arguments, however, Corry said that he has been working on the clinical application of hyperthermia since 1975. "The dilemma we face," he wrote in an e-mail, "relates to premature clinical trials run in the early eighties that showed no benefit."

Furthermore, progress in developing the technology in the U.S. depends on one company, BSD Medical Corp., in Salt Lake City, which has the only U.S. Food and Drug Administration–approved machine. But advocates say that new non-invasive technology is being tested, along with thermal nanotechnology, and that progress will be made as understanding of the biology of hyperthermia increases (see sidebar).



Rolf Issels, M.D., Ph.D.

Early Enthusiasm

Combining heat with radiotherapy or chemotherapy has had a checkered history. In the 1970s and 1980s, biological data and small clinical studies supported use of mild temperatures to increase the effectiveness of radiation, and because of that companies built devices using microwave, ultrasound, or radio frequencies to treat tumors. These devices received premarket approval from the FDA, and in 1984, the procedure was approved for insurance reimbursement. Clinical trials conducted by the Radiation Therapy Oncology Group (RTOG) followed in the 1980s and 1990s. But none showed a benefit. In one large randomized, controlled study, for example, there was little difference in response between patients who received radiation compared to patients who were treated with hyperthermia and radiation for localized tumors.

"This is. . . the first clear evidence that targeted heat therapy adds to chemotherapy."

Issues of quality control probably account for the negative trials, according to Corry and other experts. For instance, in the trial that showed no difference in response, different centers used different equipment, and 75% of the tumors treated were so large that heating the entire mass to an average of 43 °C, the standard at the time, was not possible. Also, almost one-third of the tumors treated were never tested for an internal temperature, so it was not certain the tumors were, in fact, heated. Problems with the equipment also emerged: Researchers did not know what an acceptable dose of heat was, and even if they did, the machines had difficulty maintaining a uniform tumor temperature. After an evaluation of the study, Duke's Mark Dewhirst, D.V.M., Ph.D., a pioneer of hyperthermia, said that in retrospect the design was inadequate.

Enthusiasm for hyperthermia dwindled, as did research funds and insurance reimbursement. Companies discontinued development of the devices, which were now seen as clearly flawed. Many said that the FDA's approval of the use of these devices in non-protocol settings severely tainted hyperthermia, and radiation oncologists moved on to other emerging technologies, such as three-dimensional conformal radiotherapy.

Europeans Lead

But while U.S.-based clinical studies using hyperthermia were left to a few staunch believers, such as the Duke physicians, international researchers learned from the flaws in the RTOG studies and designed their own clinical trials. Many of these have had positive results, the latest being Issels' study. A few have even shown overall survival advantages, such as the Dutch Deep Hyperthermia Trial, which found that radiation plus hyperthermia for patients with locally advanced cervical cancer improved overall survival compared to radiation alone (51% vs. 27% at 3 years); the difference was statistically significant.

Currently in Europe, a group of hyperthermia researchers are conducting several phase III clinical trials of both superficial and deep tumor hyperthermia. (In the U.S., most clinical applications and studies are using superficial therapy.) One center alone, the Erasmus MC-Daniel den Hoed

Why Would Hyperthermia Work?

The notion that heat can treat cancer is ancient. Egyptians used what they called a "fire drill" to cauterize tumors, and Hippocrates provided anecdotal evidence that cancers were susceptible to hot temperatures. In 1856, a German physician reported that a soft-tissue sarcoma was eliminated in a feverish patient.

So what is it about heat that promotes the destruction of cancer?

Heating tumors elicits a series of changes that hasten the tumor's demise, said Mark Dewhirst, D.V.M., Ph.D., of Duke University Medical Center. Heat makes blood vessels leakier and thus enables chemotherapy to penetrate the tumor more effectively. Heat also increases oxygen levels within the tumor, and oxygen is critical to the proper functioning of radiation and chemotherapy inside a cell. And heat amplifies the level of DNA damage that chemotherapy and radiation inflict upon the cancer cell by inhibiting enzymes that normally repair such damage. Also, regional hyperthermia increases blood flow to the interior of tumors, noted Roswell Park's Elizabeth A. Repasky, Ph.D., president of the Society for Thermal Medicine. That means more oxygen flow through tumors, which makes chemotherapy and radiation work better, she said.

Repasky, an immunologist, also has evidence from animal studies to support the idea that mild heat improves natural immunity to cancer as well as immunotherapy. Perhaps, she mused, heat as high as a fever or a hot tub may provide some benefit to cancer patients about to receive chemotherapy or radiation. "Now wouldn't offering patients a sauna be a nice, patient-friendly adjuvant therapy?" she asked. "We have a lot to be excited about in this field."



Mark Dewhirst,
D.V.M., Ph.D.

Cancer Center in Rotterdam, The Netherlands, treats 150 patients per year with both techniques, said one of its specialists, Jacoba van der Zee, M.D., Ph.D., a leader in the field. The center uses hyperthermia to treat cervical, breast, and head and neck cancers, as well as melanoma, all of which the group has studied. They believe it will also work in rectal and vaginal cancers, among others.

Still, van der Zee believes hyperthermia should be used more often than it is in Europe. "With all the efforts to find new treatments that are more tumor selective and less toxic, it is astonishing that an existing treatment that is relatively tumor selective, has a low toxicity, and that in clinical studies has been shown to result in considerable benefit receives so little attention," she said.

In the U.S., Duke, with the only long-term National Cancer Institute-funded project grant (23 years and running), conducts protocols with 60–80 patients each year. One randomized, controlled study with 109 breast cancer patients, published in May 2005 in the *Journal of Clinical Oncology*, demonstrated that hyperthermia combined with radiation improved response rates in patients who had recurring tumors

on the chest wall. Hyperthermia and radiation eliminated tumors in 66% of the patients, whereas radiation alone destroyed tumors in 42% of patients. The difference was statistically significant.

In June 2005, a combined analysis of three noncontrolled studies—one led by Duke researchers and the others by investigators in Norway and The Netherlands—published in *Cancer*, demonstrated that hyperthermia produced high response rates when combined with radiation and chemotherapy in advanced cervical cancer. The researchers found that 90% of patients achieved a complete remission, and after 2 years of follow-up, almost 74% of patients remained alive without signs of recurrence. On this basis, Duke attempted to launch a randomized, controlled trial but had no more patients with the advanced cancer and has had difficulties partnering with other U.S. institutions. "We were trying to give away free equipment owned by Duke to potential collaborators, but we couldn't get the trial up and running," said Vujaskovic.

Obstacles

A long-standing issue that prevents many physicians from using hyperthermia,

Dewhirst said, is that temperature can be measured only by sticking a probe inside a tumor—at least in the one machine currently approved by use in the U.S., the BSD-500. That means that the procedure demands time, attention, and training.

“The real reason it hasn’t caught on is that it is technically challenging, needing a team of people who are highly trained to do it correctly,” Dewhirst said. And with limited reimbursement, physicians, or their institutions, have no financial incentive to invest in devices, he added.

But progress in technology may change all that, he said. The FDA is considering approval of the BSD-2000, a machine that can treat deep tumors and was used in the Issels study, and Duke is conducting pilot studies looking at it in bladder cancers. One version now in testing, the BSD-200/3D/MRI, can measure heat in a tumor without a probe, Dewhirst said.

Definitive temperature measurement will lead to validation studies and accurate

guidelines for usage. “If we can crack the nut on noninvasive thermometry, that would open the door to widespread use, making hyperthermia more of a turnkey situation,” he said. Dewhirst is also working on use of liposome capsules, injected into tumors, which could release chemotherapy directly into cancer cells when exposed to heat. The technology belongs to Celsion Corp., for which Dewhirst serves as a consultant and advisor.

Reimbursement rates also seem to be climbing a bit, although they are still not where they need to be, according to Mark Hurwitz, M.D., an assistant professor at Harvard Medical School and past president of the Society for Thermal Medicine. He worked on this issue for the American Society for Radiology Oncology and found enough improvement to make the procedure more financially viable.

“If the reimbursement issues could be resolved, most of the rest of the roadblocks would follow suit,” said the University of Arkansas’ Corry. “Equipment manufac-

turers would jump on the bandwagon, as they have for the incredibly expensive proton and heavy-ion therapy, which are reimbursed.”

In 2009, as of late September, BSD Medical Corp. had sold five BSD-500 hyperthermia systems in the United States and two internationally. One center that purchased the device was the University of California, San Francisco, Medical Center, which promotes itself as having “the largest and most versatile hyperthermia program on the West Coast.” I-Chow (Joe) Hsu, a radiation oncologist at UCSF, said hyperthermia is particularly useful for treatment of recurrent cancer in an area of the body that has already received radiation therapy. “The biology behind its use is compelling, and adding hyperthermia to radiation doesn’t increase toxicity,” he said. “It’s a free ride in that regard, and we should take advantage of it.”

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