In late January 2010 the Journal of the National Cancer Institute (JNCI) came out with a highly positive article on hyperthermia or heat therapy (Twombley 2010). The stimulus for the article was a positive clinical trial with local hyperthermia in sarcoma reported at the European Society of Medical Oncology meeting in Berlin last fall. This randomized trial showed that patients given chemotherapy plus hyperthermia had a median disease-free survival of 32 months, whereas those who got chemotherapy alone had a survival of 18 months. Although this difference was statistically significant, there was no significant difference in overall survival. The most frequent side effect of hyperthermia (104 to 109°F) was "mild to moderate discomfort" (in 45 percent) whereas the most serious side effect was a severe burn seen in one patient (0.6 percent).

The lead investigator of that trial, Rolf Issels, MD, PhD, said that the treatment provided a "new standard treatment option." However, Issels continued, "the implications of these findings are more far-reaching. This is also the first clear evidence that targeted heat therapy adds to chemotherapy."

In the US, as well, long-time investigators of hyperthermia hailed the findings. "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 research and clinical use of hyperthermia.

Others expressed skepticism about the actual impact of the sarcoma trial. "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, a leading center of hyperthermia research, is the only US institution that participated in the Issels study.

The JNCI author, Renee Twombley, tries to provide some explanations for the neglect of hyperthermia, particularly in the US. These are basically (1) the technical demands of operating the hyperthermia equipment; (2) the current FDA requirement that probes be inserted into tumors in order to accurately measure temperatures; and (3) and "the historically low insurance reimbursement rates."

The lack of what Twombley calls "abundant evidence" that the treatment can affect overall survival also plays a role. This explanation avoids the question of why other cancer treatments, such as the drug Avastin (bevacizumab) for breast cancer, have also not been shown to affect overall survival, yet are approved by the FDA and by the oncology community as a whole.

"The dilemma we face," said researcher Peter Corry, PhD, "relates to premature clinical trials run in the early eighties that showed no benefit."

Another problem is that there is presently only one manufacturer of hyperthermia equipment in the US, BSD Medical Corp. of Salt Lake City. Advocates point out that there is a greater choice of innovative machinery available in Europe, as well as new thermal nanotechnology that may lead to breakthroughs in the field. (BSD's stock soared 37 percent, albeit temporarily, upon publication of the JNCI article.)

The article detailed the "checkered history" of hyperthermia with radiation or chemotherapy. In the 1970s and 1980s preliminary reports of benefit supported the use of mild temperatures to increase the effectiveness of radiation. Various devices using microwave, ultrasound or radio frequencies were built to treat tumors. These received pre-market approval from the FDA and in 1984 hyperthermia was approved for insurance reimbursement.

TO BE COMPLETED, WITH REFERENCES, NEXT WEEK

--Ralph W. Moss, Ph.D.

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LAST WEEK WE BEGAN A TWO-PART NEWSLETTER ABOUT THE JNCI HYPERTERMIA ARTICLE. WE CONCLUDE THIS WEEK.

In 1984 hyperthermia was approved for insurance reimbursement. Then came some major setbacks. Clinical trials conducted by the Radiation Therapy Oncology Group (RTOG) failed to show clinical benefit. In one large randomized, controlled study 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 was a body blow to hyperthermia (Perez 1991; also Emami 1996).

Amazingly, however glaring issues of quality control could probably account for the negative result, according to researcher Peter Corry, PhD. For instance, in the aforementioned trial, different centers used different equipment, and 75 percent of the tumors treated were so large that heating the entire mass to an average of 43\(^\circ\) C, the standard at the time, was not possible.

Also, says the JNCI, almost one-third of the tumors that were treated were never tested for an internal temperature, so it was not certain that the tumors in question were ever actually heated! Problems with equipment and technique also emerged in the course of the trial. The machinery had difficulty maintaining a uniform tumor temperature and, in any case, researchers did not know what was an effective dose. Mark Dewhirst, DVD, PhD, of Duke University has reviewed the study and said that the design was clearly inadequate.

But the negative study had its effect. The general enthusiasm for hyperthermia (once called oncology's fourth modality) soon dwindled, as did the research funds and insurance reimbursement. Companies stopped making the devices, which in any case were probably ineffective. In fact, many of today's researchers blame the FDA for approving these devices for use in general practice, which in their eyes severely tainted hyperthermia. Most critically, radiation oncologists moved on to other emerging technologies, such as three-dimensional conformal radiotherapy. Few people wanted to associate themselves with what was perceived as a dead or dying field.

Once again, Germany and its neighbors lead the way. While Americans largely deserted the field, the Germans learned from the failed trials and continued to improve their equipment and their study designs. Last year the Dutch Deep Hyperthermia Trial found that radiation plus hyperthermia improved overall survival compared to radiation alone (51 percent vs. 27 percent at 3 years) for patients with locally advanced cervical cancer. It was a hugely important finding—demonstrating in a rigorous way that hyperthermia does indeed significantly increase (in fact, nearly double) survival in a major form of cancer.

Jacoba van der Zee, MD, PhD, is a Dutch leader in the field. She uses hyperthermia to treat cervical, breast, and head and neck cancers, as well as melanoma. They also believe it will also work in rectal and vaginal cancers. Van der Zee reflects the widespread European belief that hyperthermia should be used more often than it is now.

"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.

The American immunologist, Elizabeth Repasky, PhD, went even further, raising the possibility of using hot baths saunas to raise temperatures in conjunction with standard therapies. (One origin of hyperthermia was
the once-popular "Schlenz bath" of the 1930s and 1940s.)

Repasky has evidence from animal studies that mild heat improves natural immunity to cancer as well as immune function. Perhaps, she told JNCI, fever-range heat 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."

There are important lessons to be gained from this history of hyperthermia. One of them is that you should never rule out a therapy because of one or two negative randomized controlled trials (RCTs). Oftentimes there are flaws in the methodology or conduct of these trials that leads to negative results. In the case of hyperthermia, it took the sympathetic and intelligent guidance of Rolf Issels, et al., to finally show the power of this "patient-friendly" modality.

---Ralph W. Moss, Ph.D.

References:


