Dilemma in Cancer Treatment

Physicians are placed in a difficult position by suggestions that widely used chemotherapies may not be useful in osteogenic sarcoma

Nearly every current list of curable cancers includes osteogenic sarcoma. This cancer of the long bones of the arm and leg primarily strikes teenagers, and, until recently, its prognosis was dismal. In the 1960's, virtually everyone who got the disease died within 2 years. Now as many as 50 percent of those whose cancer has not spread at the time of diagnosis are cured, and as many as 70 percent of all patients live 2 years.

Whenever such a dramatic change in cancer survival rates occurs the question is, why? Most pediatric oncologists used to think they knew the answer, but now many are not so sure. As a result, they are confessing that they no longer know how to treat their osteogenic sarcoma patients.

The conventional wisdom has been that adjuvant chemotherapy, which is chemotherapy given to patients with no evidence of metastasis at the time of diagnosis, helps cure osteogenic sarcoma patients. The idea is that the treatment destroys micrometastases—tiny foci of cancer that cannot be visually detected. Adjuvant chemotherapy is thought to make metastases less likely to develop and, if they do, less numerous and easier to treat. The chemotherapy is always preceded by removal of the cancerous bone.

Prior to the 1970's osteogenic sarcoma patients were treated with surgery alone. Adjuvant chemotherapy was not given because there was no reason to believe that it would help. Those who already had metastases at the time of diagnosis often were not treated at all—their situation was considered hopeless. The prognosis for these patients is still not particularly good, although now they are given chemotherapy and their metastases (which nearly always occur in the lungs) are surgically removed. But these patients often are not cured. The crucial step in curing osteogenic sarcoma, members of the medical community believe, is in preventing it from spreading through the body—which adjuvant chemotherapy was said to do. This chemotherapy was thought to have been a key factor in the difference between the survival rates for the 1960's and those for the 1970's.

Yet all along there were those who doubted that the case for adjuvant chemotherapy was established. A few investigators, primarily at the Mayo Clinic and the National Cancer Institute (NCI), were suspicious that, because of changes in diagnostic techniques, the pre-1970 patients could not fairly be compared with patients today. Thus, it was felt, the comparisons in survival rates that established the usefulness of adjuvant chemotherapy might be misleading. Perhaps, they said, adjuvant chemotherapy really is not helpful in treating osteogenic sarcoma. The method is toxic and very expensive; it would be of grave concern if it were given needlessly. Until recently, however, the skeptics were given short shrift. "The desire to believe in progress in cancer treatments is so profound that people don't want to hear the disbelievers," says Arthur Levine, who heads the pediatric oncology branch at the NCI.

The story of how adjuvant chemotherapy became an accepted treatment for osteogenic sarcoma and why it is now being questioned illustrates statisticians' worst fears about the use of historical control groups in clinical medicine. It also illustrates the agonizing dilemmas that can occur when doubts are raised about an apparently successful treatment. These dilemmas are commonplace, says Vincent DeVita, acting director of the NCI, and they arise nearly every time there appears to be progress in cancer treatment. Frequently, it is not clear which of several factors is responsible for the encouraging results.

Because osteogenic sarcoma had such a grim prognosis in the 1960's, medical researchers began trying one chemotherapeutic agent after another in an attempt to destroy lung metastases. Nothing worked. Then, in the early 1970's, two new chemotherapeutic agents were tried —adriamycin and high doses of methotrexate. Initial reports were that as many as 80 percent of the patients with metastatic disease responded. Oncologists were ecstatic over these results. "Everyone went bananas," says Herbert Abelson of Harvard's Sidney Farber Cancer Center. But, as more patients were given this chemotherapy, it became clear that really only a small percentage respond, and then only temporarily.

Caught up on the initial wave of excitement over adriamycin and high-dose methotrexate, James Holland at Mount Sinai Medical Center and, independently, Norman Jaffee, now at the M. D. Anderson Cancer Center in Houston, together with Emil Frei of the Sidney Farber Cancer Center tried using these same chemotherapeutic agents *before* the disease had obviously spread. In 1974, the two groups reported that about 50 percent of patients who had no evidence of metastases and who were treated with adriamycin or high-dose methotrexate lived disease-free for 2 years after their disease was diagnosed. In contrast, only 20 percent of the 1960 patients with no evidence of metastases at the time of diagnosis lived 2 years.

Since 1974, adjuvant chemotherapy has been given in increasingly higher doses. A variety of chemotherapeutic agents has been tried, alone and in combination, but still the most commonly used ones are adriamycin and high-dose methotrexate. Since methotrexate, a folic acid antagonist that prevents DNA synthesis, is extremely toxic when given in high doses, it must be followed by calcium leucovorin, a folic acid analog that allows normal cells to survive. Both methotrexate and adriamycin cause vomiting and hair loss and both can also have more serious side effects. For example, adriamycin can damage the heart, leading to a form of congestive heart failure. There is a maximum cumulative dose of the drug that patients can tolerate in their lifetime.

At the same time as adjuvant chemotherapy was becoming popular, diagnostic techniques were changing. In the 1960's, physicians used chest x-rays to look for metastases. In the 1970's, they switched to the more sensitive technique of chest tomograms, which are x-ray slices of the chest. More recently, a number of medical centers have begun using the even more sensitive tech-

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nique of computer-assisted tomography.

These changes in diagnostic technique put a question mark over the use of historical control groups. There is a real danger that many of the 1960 patients who were supposed to have been free of metastases might actually have had metastatic disease by 1970 criteria.

Among those who raised these questions about the patient comparisons were investigators at the Mayo Clinic. In 1976 they asked for and received funds from the NCI to conduct a randomized controlled trial comparing adjuvant chemotherapy plus amputation to amputation alone for patients with no visible metastases at the time of diagnosis. The investigators felt that such a trial was warranted for theoretical reasons and because they had just reviewed their data on the survival rates of patients with osteogenic sarcoma. The results were illuminating.

Between 1963 and 1972, they found, the survival of patients at the clinic who had no metastases at the time of diagnosis and who were treated with amputation alone was typical of that at other institutions—about 25 percent lived 2 years after the disease was diagnosed. But from 1972 to mid-1974, the 2-year disease-free survival rate had increased to 50 percent, typical of the rate claimed for patients given adjuvant chemotherapy, even though most of the Mayo Clinic patients had not been given this chemotherapy. "The survival of patients treated with surgery alone is excellent and is getting better all the time," says William Taylor, a Mayo Clinic statistician.

There is no obvious explanation for the Mayo Clinic's experience. "When I look at the data, the dominant variable is still time," Taylor remarks. Other institutions cannot do a similar analysis of survival rates, since they have given patients adjuvant chemotherapy for nearly a decade.

Although the more sensitive diagnostic techniques for detecting lung metastases could have contributed to the improved survival rates of Mayo Clinic patients, it is not yet clear just how many patients with metastatic disease who are now being screened out of study groups would previously have been included. Steven Rosenberg, chief of surgery at the NCI, says that 4 of 11 osteogenic sarcoma patients who had normal chest x-rays were found to have metastatic disease upon referral to the NCI. John Muhm and Douglas Pritchard of the Mayo Clinic report that 20 percent of their patients who have no metastases detectable with chest x-rays have metastases detectable with CAT scans and that 15 percent of patients with no metastases detectable with tomograms have visible metastases when given CAT scans. On the other hand, Jaffee finds that tomograms only detect an additional 3 percent of patients with metastases. "I don't think screening methods make a difference," he says.

Even the Mayo Clinic patients who relapsed, however, seemed to live longer in the 1970's than in the 1960's. The improved survival times obviously were not due to adjuvant chemotherapy, but may have occurred because surgeons in the 1970's began removing lung metastases. They discovered that this process seemed to prevent further relapses. DeVita recalls that in the days before this surgery was tried, "I used to go on the wards and see the osteogenic sarcoma patients. Anyone with metastatic disease was considered gone." Surgeons began removing lung metastases, DeVita says, because the patients were young, their situation seemed hopeless, and the surgeons were anxious to do something to help them. No one expected the surgery to do much good. "It was contrary to the theory of metastatic disease," DeVita explains. Physicians generally believe that once a cancer has spread, the visible metastases are only part of the cancer. Microscopic metastases are also thought to be present and these cannot be removed.

Another possible reason for the improved survival rates is that the patient referral patterns changed in the 1970's. The 1960 patients, DeVita explains, "probably reflected a smaller proportion of patients. The minute there was excitement about adjuvant chemotherapy, more patients were referred [to major medical centers]. This always happens when you make some progress." It is conceivable that before the excitement over adjuvant chemotherapy, most of the patients referred to major medical centers were those with the worst prognoses.

These possible explanations of the Mayo Clinic's finding that the clinic patients treated without adjuvant chemotherapy seemed to do well were reasons to conduct a randomized controlled trial, in the opinion of a number of medical investigators. But the Mayo Clinic's trial was not well accepted by many physicians who believed in adjuvant chemotherapy and thought the trial unethical. The Mayo Clinic physicians had great difficulty recruiting patients for their randomized controlled trial. They ended up with only 37 patients, which is less than half the number referred to the clinic and asked to participate.

Some patients, explains John Edmonson, who conducted the Mayo Clinic trial, declined to participate because they decided they definitely wanted chemotherapy. Often these patients were swayed by their personal physicians, who told them that all major medical centers except the Mayo Clinic believe in adjuvant chemotherapy for osteogenic sarcoma. Other patients did not participate because, after being told by the Mayo Clinic investigators that there was some question about whether adjuvant chemotherapy works, that the therapy is toxic, and that they would have to come to the clinic every 3 weeks for 1 year and spend 3 to 5 days there each time, the patients decided that they would rather take their chances without chemotherapy.

The trial went ahead anyway, and Edmonson presented preliminary results at the end of May at a meeting of the American Society of Clinical Oncology. More than half the trial's patients, he reported, were continuously disease-free 2 years after surgery, and 75 percent survived 2 years. There was no difference between the treatment groups in time to first metastasis, and there was no difference between the groups in number of metastatic nodules appearing at relapse. Still, 37 patients is a very small number. "These results cry out for corroboration," Taylor says.

The Mayo Clinic results, however, have not been enthusiastically embraced by all oncologists. "We hurt a lot of people's feelings. This is not something people take lightly," said Edmonson. Others, however, say it is not that their feelings are hurt. Rather, they remain unconvinced by this trial. First, they say that only the Mayo Clinic reports such good survival data for patients not given

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adjuvant chemotherapy. "What is different about the Mayo Clinic population?" asks Charles Pratt of St. Jude's Hospital in Memphis. He points out that the patients are mostly white, middle- or upper-middle-class, and may receive treatment earlier in the course of the disease than poorer patients from urban areas or the rural South.

Abelson points out that it is hard to draw conclusions about a trial consisting of only 37 patients. This is not to fault the Mayo Clinic—only about 1000 people in this country develop osteogenic sarcoma each year. But in order to detect a 20 percent difference in survival between two groups, a trial would have to include at least 180 patients, according to Abelson. Even then, he says, there would still be a 5 percent chance of a false negative. "It is patently impossible for a single institution to do [an appropriately sized] study. It's almost mandatory to do a multi-institutional trial."

The NCI has been trying for several years to interest other institutions in joining it in a controlled trial of adjuvant chemotherapy in osteogenic sarcoma. Until very recently, it has had no success. Following the announcement of the Mayo Clinic results, however, six institutions are willing to consider joining the NCI in such a trial, Levine says. Abelson, who is among those now interested in a controlled trial, explains that he believes a trial is warranted because "the historical control problem is so substantial and the issues raised are so provocative." Others, as would be expected, believe so strongly in adjuvant chemotherapy that they feel ethically constrained from participating in such a trial. "I would not like my patients entered in such a trial," says Jaffee.

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Tapping Sun-Warmed Ocean Water for Power

A successful experiment boosts ocean thermal energy into favor, but hurdles remain to commercialization of the process

Late last summer, in an experiment near Hawaii, usable power was generated for the first time from temperature differences in ocean water. This successful demonstration of ocean thermal energy conversion (OTEC) triggered enthusiasm for the process. President Carter just signed into law two measures to spur OTEC research and speed commercialization.* Yet OTEC remains a hope, not a firm solution for the energy crisis. Although the experiment showed that OTEC can produce electricity, it did not prove that commercial-sized plants, generating a few hundred megawatts, could run continuously for many years, providing power at a competitive price.

This is one of a series of occasional articles about the prospects and problems of alternative energy sources.

The appeal of OTEC is that its fuel—sun-warmed ocean water—is free and virtually unlimited. Oceans in the tropics are heated so much that in theory they could provide several times more electricity than is consumed in the world. The temperature difference of 20° to 25°C between surface and deep water can operate a heat engine to generate electricity.

The critical question is whether it is feasible to extract the free energy for a reasonable price. Building commercial OTEC plants will be a major challenge, as many components are huge. Furthermore, keeping the plants operating in the harsh marine environment may be overly expensive. Storms, waves, and marine organisms growing on equipment can all threaten an OTEC facility.

Although the United States is shy of warm territorial waters, the Department of Energy (DOE) is enthusiastic about OTEC's potential to fill a significant portion of the world's energy needs. About 5 percent—$37 million—of DOE's solar energy budget funds OTEC research and development. For U.S. use, electricity from OTEC could be cabled to shore in Hawaii, Puerto Rico, Guam, the Virgin Islands, and along the Gulf Coast. Moreover, energy-intensive products could be manufactured in the tropics with OTEC energy and shipped to shore, says William Avery, head of an OTEC research group at Johns Hopkins University. Ammonia manufacturers, currently heavy consumers of natural gas, are eager to move to sea, according to John Babbitt, president of DEVCO in Tulsa and one of the founders of Solaramco, a newly formed consortium of ammonia manufacturers interested in OTEC.

When last summer's experiment worked, it boosted OTEC into favor: for the first time the prospects for OTEC appeared to outweigh the problems that have colored researchers' perspectives of the process in the past (*Science*, 14 October 1977). The plant, dubbed Mini-OTEC, was launched by Lockheed Missiles and Space Company, the Dillingham Corporation, Alfa-Laval Incorporated of Sweden, and the state of Hawaii, with no federal funding. "Fifteen months after the four parties shook hands on the agreement [to cosponsor the $3 million experiment], we had net power generation," says Roger Fuller of Lockheed. Roughly 40 of the 50 kilowatts generated were used to power the plant, leaving 10 kilowatts to light some flood lamps.

"Once Mini-OTEC started up, it ran and ran. There was nothing for us to do but go fishing," relates Fuller. Housed on a surplus barge loaned by the Navy, the plant worked as well as or better than its designers predicted. Moreover, none of the problems touted by OTEC skeptics interfered with the generation of electricity.

Mini-OTEC is a miniaturized version of what is envisioned as a first-generation OTEC plant. Warm water from the ocean surface evaporates ammonia. The vapor expands through a turbine and is then condensed by cold seawater pumped through a pipe from a depth of nearly 700 meters. In Mini-OTEC, the turbine drives a 50-kilowatt generator.

Although Mini-OTEC was built hurriedly with off-the-shelf components, it surprised skeptics by generating net power. But, as anticipated, the yield was not very high: 80 percent of the electricity was needed to operate the plant, primarily to pump the seawater. A carefully designed plant built of components specifically suited to OTEC should do much better, leaving perhaps 65 to 70

*On 17 July President Carter signed the Matsunaga-Fuqua Bill (OTEC Research, Development, and Demonstration Act), which establishes goals for OTEC research and mandates that OTEC plants be producing 10,000 megawatts by 1999. The Studds-Inouye Bill (OTEC Act of 1980) was signed into law on 3 August. It sets up licensing regulations for OTEC plants and establishes a loan guarantee program to aid their construction.

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