Unproven Methods of Cancer Management

Laetrile

After study of the literature and other available information, the American Cancer Society has found no evidence that Laetrile results in objective benefit in the treatment of cancer in human beings. Lacking such evidence, the American Cancer Society strongly urges individuals with cancer not to seek treatment with Laetrile.

The following is a review and summary of material on Laetrile in the American Cancer Society files as of July 1990. Reference to that material by the Society does not imply agreement with its contents.

Abstract

"Laetrile" is used interchangeably with "amygdalin" to designate natural substances, derived primarily from apricots and almonds, that can release cyanide, which is lethal to living organisms. In the 1920s, Dr. Ernst T. Krebs, Sr., formulated a theory that amygdalin could kill cancer cells. His theory was inconsistent with biochemical facts and has since been modified at least twice by his son, Ernst T. Krebs, Jr.

Extensive work has been done by cancer scientists to test the claim that Laetrile fights cancer. Many animal experiments in the 1970s showed a complete lack of tumor killing by Laetrile. Reviews of the medical records of patients whose cancers were claimed to be reduced or cured after Laetrile treatment found insufficient medical evidence to judge Laetrile's efficacy. Finally, in a clinical trial in cancer patients reported in 1982, Laetrile neither caused shrinkage of tumors, nor increased survival time, nor alleviated cancer symptoms, nor enhanced well-being.

Several reports in the medical literature document instances in which Laetrile has caused serious, life-threatening toxicity when taken in large doses in the manner prescribed by Laetrile advocates. In light of the lack of efficacy of Laetrile and its demonstrated ability to cause harm, Laetrile should not be used to treat cancer.

What Is Laetrile?

Because the term Laetrile has been applied to various substances for four decades, it is helpful to clarify the current meaning of the word. Interchangeable use of the terms "Laetrile," "amygdalin," and "vitamin B-17" has compounded the confusion. The following information is taken from reports by the American Cancer Society,[1] the Food and Drug Administration (FDA),[2] Dorr and Paxinos,[3] Herbert,[4] and Wilson.[5] A 1980 book by Young offers further historical data.[6]

In the 1920s, Dr. Ernst T. Krebs, Sr., a German immigrant living in San Francisco, tested an orally administered extract of apricot kernels for medical purposes. He found it too toxic for human use, since it contained amygdalin, which is converted by intestinal bacteria to the poison cyanide.

In 1952, Dr. Krebs' son, Ernst T. Krebs, Jr., produced a supposedly less toxic form of amygdalin, for which he coined the term "Laetrile." In amygdalin, two glucose molecules are linked to the compound mandelonitrile. In the substance

made by Krebs, Jr., mandelonitrile is linked to one sugar molecule. In addition, the chemical bonds by which the sugars are joined differ between the two compounds. These differences become crucial when the proposed mechanism of action of Laetrile is considered (see below).

What is actually used in Laetrile therapy is amygdalin. Chemical analysis of commercial Laetrile reveals essentially amygdalin.[2,3,7,8] In addition, the terms amygdalin and Laetrile are used interchangeably in many documents produced by Laetrile proponents and on labels of the purported medicine. In this document, "Laetrile" will mean "amygdalin."

Vitamin B-17 is the name given by Krebs, Jr., in 1970 to a group of compounds encompassing both amygdalin and the derivative that he made.

Postulated Mechanisms of Action

Initially, it was claimed that Laetrile kills tumor cells through the action of the enzyme beta-glucosidase. Beta-glucosidase splits compounds such as amygdalin, in which two sugars are joined in a glucoside bond. In this theory of Laetrile's action, the action of beta-glucosidase releases mandelonitrile, which produces cyanide, killing nearby cells.

Laetrile proponents assert that cancer cells are selectively killed for two reasons: beta-glucosidase is much more abundant in cancerous tissues; and cancer cells are deficient in another enzyme, rhodanese, which promotes rapid breakdown of cyanide to a harmless chemical. These two factors would cause a buildup of cyanide around cancer cells.

However, neither of these assertions is true.[2,9] Analysis shows only traces of beta-glucosidase in animal tissues. Moreover, rhodanese levels are equal in normal and cancerous tissues. In 1955, in response to these objections, Dr. Krebs and Krebs, Jr., modified their theory to propose that it is the enzyme beta-glucuronidase, rather than beta-glucosidase, that is more abundant in cancer tissues. If this were true, the compound devised by Krebs, Jr., in 1952 would release cyanide in cancer tissues, since it contains a glucuronide bond.

There are two fallacies to this thesis, however. First, beta-glucuronidase is no more abundant in malignant than in healthy tissues.[3] Second, this theory is irrelevant to the preparations of Laetrile used, which contain amygdalin.[2,3,7,8] Beta-glucuronidase does not act on amygdalin, because that substance contains a glucoside bond.

In 1970 Krebs, Jr., advanced an entirely different theory—that cancer is a vitamin-deficiency disease and that it can be prevented by Laetrile, which he dubbed vitamin B-17.[10] This idea was apparently an attempt to get around the FDA regulations, which apply to medicines but not to vitamins. However, there is no evidence that amygdalin meets the standards for a vitamin.[11,12] Amygdalin has not been shown to be required to achieve health, nor has any disease been associated with its absence.

Investigations Into the Anticancer Efficacy of Laetrile

Although it is important to understand what Laetrile is and how it is supposed to work, the pivotal practical issue is whether there is any evidence suggesting that it has anticancer efficacy. Scientific studies were conducted for more than 20 years, starting in the mid-1950s, looking for evidence of antitumor efficacy by Laetrile. In no instance was evidence found that treatment with Laetrile results in any benefit against tumors in animals. Despite this negative record, a clinical trial in humans was conducted in 1981. It did not show any anticancer effect of Laetrile. The following chronology is from the National Cancer Institute.[13]

Animal Experiments

Starting in 1957 Laetrile was repeatedly tested against tumor cells implanted in animals. At least a dozen separate sets of experiments were done at seven institutions. Targets included a variety of transplantable tumors, including carcinoma, leukemia, sarcoma, lymphoma, and melanoma cells. Laetrile was tested alone and combined with beta-glucosidase. Different sources of amygdalin were used, including material

from the McNaughton Foundation, a pro-Laetrile organization.

In all experiments objective criteria of tumor growth were used, either quantitative measurement of tumor size in two dimensions or survival or both. Results were always compared in a blinded fashion with a control group and in some cases with a known positive anticancer drug. In no case was any antitumor activity detected with Laetrile.[13–19]

In 1975, Laetrile advocacy groups claimed that positive results had been obtained in experiments at Memorial Sloan-Kettering Cancer Institute. These experiments were not blinded and were based on visual estimation, rather than quantitative measurement, of metastatic growth. Further double-blind experiments that used an objective bioassay for metastatic growth were negative.[18]

Case Reviews

Despite the lack of evidence for the efficacy of Laetrile, the NCI evaluated it through a retrospective case review. This was not the first such review, however.[2] Analyses of patient records submitted by pro-Laetrile groups had been done by committees of the California Medical Association and the California Department of Public Health. In addition, the FDA had conducted a joint investigation with the NCI of 12 clinical histories submitted by Dr. Ernesto Contreras, head of a Laetrile clinic in Tijuana, Mexico.

In all these reviews, experts concluded that the records did not support claims of therapeutic benefit from Laetrile. In some cases there was no pathologic proof of malignancy, and follow-up was often too short to draw any conclusions. Many cases included little or no objective evidence of disease response, and most patients had received conventional therapy as well as Laetrile.

Despite these unpromising precedents, in January 1978 the NCI went to great lengths to carry out a case review incorporating strict design and evaluation criteria. Requests for apparently positive cases were sent to 385,000 US physicians and 70,000 others, for a total of 455,000 letters. There were also direct requests for cases to pro-Laetrile groups. Although it was estimated that Laetrile had been taken by 75,000 Americans at that time,[20] only 93 "positive" outcomes were submitted.

Twenty-six cases lacked adequate documentation, such as convincing cancer diagnostic procedures or objective follow-up assessment.

Review of the remaining 67 cases was stricter than prior analyses. (There were 68 records because one patient had two distinct courses of Laetrile therapy.) Records were mixed with those of 67 patients treated by chemotherapy and then submitted to a panel of 12 oncologists who did not know which patients had received which treatment. In 62 cases the panel saw no response to Laetrile therapy. Two complete and four partial responses were seen among the Laetrile cases, which allowed "no definite conclusions [about] the anti-cancer activity of Laetrile."[21]

Equally important, the panel wrote, "This retrospective analysis illustrates the difficulty of drawing inferences about therapeutic efficacy in the absence of properly designed trials."[21]

A Clinical Trial of Toxicity/Dosage And Efficacy

To resolve this indeterminate situation, the NCI formulated plans to test Laetrile in cancer patients at four US cancer centers. In December 1979, the FDA granted the NCI an Investigational New Drug (IND) status for Laetrile to do a toxicology study of Laetrile and to test its antitumor effectiveness and its ability to alleviate cancer symptoms (pain, weight loss, and lack of well-being).

In the toxicity trial, six patients who had untreatable cancer but who were ambulatory and maintained oral food intake were treated sequentially with intravenous followed by oral amygdalin. The purity of the amygdalin used was established to be 99 percent by several assays. No toxic effects were seen in five patients.[32] The sixth patient showed clinical evidence of cyanide toxicity after eating large amounts of raw

almonds, which contain beta-glucosidase, along with amygdalin. Foods containing beta-glucosidase are typically prescribed by Laetrile practitioners.

The efficacy trial was designed to be representative of prevailing Laetrile practice, based on writings by some Laetrile practitioners and consultation with others. Laetrile treatment was combined with an overall metabolic therapy program consisting of vitamins A, C, and E; vitamin B complex with minerals; and pancreatic enzymes. Since practice varied, two doses of amygdalin (the high dose was about 1.5 times the standard dose) and vitamins were used. Diet was restricted with regard to many items, including eggs, meat, refined-flour products, caffeine, and alcohol. Fresh fruits and vegetables and whole grains were emphasized.

The Laetrile used was prepared from apricot pits and corresponded to the products distributed by the major Mexican supplier of Laetrile, American Biologics. Its purity was established by extensive assays.

Patient selection favored detection of any therapeutic activity of amygdalin. All 178 patients were ambulatory and able to eat. One third had had no chemotherapy, and all had been off conventional therapy for at least one month. Seventy percent of the patients were still able to work.

Evaluation included tumor measurements before treatment and several times thereafter and measurements of body weight, activity level, and symptoms. In three months, disease had progressed in 90 percent of patients. By eight months, 80 percent were dead. These results are similar to those found with no treatment. A subgroup of colorectal cancer patients in the Laetrile trial were compared with a group of similar patients who had been treated with agents that turned out to be ineffective. Survival curves for the two groups were identical.[23]

The authors wrote, "No substantive benefit was observed in terms of cure, improvement, or stabilization of cancer, improvement of symptoms related to cancer, or extension of life span."[24] This trial showed unequivocally that Laetrile is ineffective for cancer therapy.

In a letter responding to criticism that the trial should have included a control group treated with standard therapy, the senior author, Moertel, pointed out that in testing potential anticancer drugs a comparative trial is done only after a substance has shown evidence of therapeutic efficacy. "It would be unconscionable to randomize people between a drug [with no evidence of therapeutic effect] and standard therapy that would hold a known potential for cure or [life] extension," he wrote.[23]

Thus, the results of animal studies and several retrospective case history reviews failed to provide any evidence for an antitumor effect of Laetrile or for its claimed ability to provide benefit to persons with cancer. In addition, a prospective clinical trial demonstrated conclusively that Laetrile is of no benefit to cancer patients.

Toxicity of Laetrile

Given the lack of efficacy of Laetrile, there is no justification for running any risk from taking it. There is in fact a small but finite danger associated with Laetrile use. Several case reports have described serious or lethal toxicity from Laetrile ingestion. Some have involved overdoses inadvertently taken by infants. Braico et al[25] reported the death of an 11-month-old child following ingestion of one to five 500-mg Laetrile tablets. The father "considered the pills to be harmless vitamins." Ortega and Creek[26] described a three-year-old child who suffered near-fatal cyanide poisoning after being given three Laetrile enemas in one day. Hall et al[27] described a four-year-old child who almost died of cyanide poisoning from ingesting Laetrile but who recovered when treated with an antidote.

Even more significant are cases of cyanide toxicity in adults taking oral Laetrile in recommended doses. Two patients taking oral Laetrile (one and three 500-mg tablets a day) were reported by Smith et al.[28] In one, cyanide toxicity manifested as "progressive neuromuscular weakness of both lower and upper extremities as well as bilateral ptosis." In the other, respiratory arrest was seen. Symptoms in both patients resolved when Laetrile was discontinued.

Similar incidents of respiratory distress were described by Barnett et al[29] and Morse et al.[30]

Herbert[4] related the case history of a woman in California who died after being seen in an emergency room. Because the woman was not under a physician's care, an autopsy was required. A cyanide odor arose from the incision, and cyanide was found in her blood and stomach. It was discovered that she had been taking one gram per day of Laetrile orally with crushed apricot kernels, which promote transformation of Laetrile to cyanide. Without an autopsy, this death might have been attributed to the cancer.

Kalyanaraman et al[31] reported a neuromyopathy, with demyelination and axonal degeneration, in a 67-year-old woman with lymphoma who had been treated with Laetrile. High cyanide levels were found in her blood and urine. Clinical improvement followed cessation of Laetrile usage.

Cyanide intoxication is a risk only when Laetrile is taken orally. Beta-glucosidase made by bacteria in the intestine decomposes amygdalin to cyanide; with intravenous Laetrile, the usual treatment method, most is excreted in the urine without releasing cyanide.[21,32] Thus, intravenous Laetrile can have no therapeutic effect.

Legal Status of Laetrile

Laetrile has been the focus of extensive litigation. The most important case was Rutherford v. USA, in which US District Court Judge Luther Bohanon ruled in 1977 that the FDA had acted illegally in seizing shipments of Laetrile. He enjoined the FDA from further seizures. The case was appealed to the US Supreme Court, which overturned the injunctions in 1979. The Supreme Court ruled that the FDA's enforcement of safety and efficacy must apply to terminally ill patients as well.[33]

Separate from his court decree, Judge Bohanon had set up a system under which a patient could get Laetrile for personal use if a physician signed an affidavit that the individual was terminally ill. This "affidavit system" was not undone until 1987. During this period 27 state legislatures passed laws making it legal to use Laetrile within the state. Such laws remain in more than 20 states.

As a result of the Supreme Court's 1979 ruling, it is now illegal to transport Laetrile across state lines or from another country into the United States, even with a physician's affidavit. It is also illegal to use Laetrile in states that have no explicit law allowing it.

Laetrile is currently used as one component of "holistic" regimens, which emphasize cure through purification and the body's capacity to heal itself.[34] According to a directory of alternative clinics,[35] several such clinics in Tijuana and the US list Laetrile as one element in "metabolic" regimens with peroxide, enemas, high-protein diets, mind control, and other "natural" approaches.

Conclusion

In 1977, after an extensive review of information about Laetrile, FDA Commissioner Donald Kennedy concluded, "This review has affirmed my conviction that Laetrile is a major health fraud in the US today [and] that there is no evidence of its safety and effectiveness."[2] In the 12 years since Commissioner Kennedy wrote those words, the only new evidence concerning Laetrile has demonstrated its toxicity and lack of efficacy even more convincingly. In 1982, the study by Moertel et al concluded that "amygdalin (Laetrile) is a toxic drug that is not effective as a cancer treatment."[24] The American Cancer Society concurs in this judgment.

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