Case Report

Metastatic colorectal cancer and Laetrile in the 21st century: persistence of a 1970s controversy

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Abstract: In this case report, we present a common gastroenterological complaint with a unique twist discovered in taking a thorough medical history: a 48-year old man with a history of metastatic colorectal cancer, presented with an upper GI tract bleed. He had recently begun taking Vitamin B17, an alternative therapy purchased in Mexico marketed as an anti-cancer medication. This vitamin is a previously popularized, but ultimately de-bunked and banned substance better known as laetrile. Laetrile was adopted as an alternative cancer therapy in the 1950's. It was marketed based on small Best Case Series documenting Laetrile-related symptomatic benefits. There have been no randomized clinical trials performed. Twenty years later, Laetrile was banned following multiple reports of toxicity and death. Laetrile use in the 21st century is particularly unique and provides us with an opportunity to reflect on the importance of clinical trials and evidence-based medicine, which guides our daily practice.

Keywords: Laetrile; amygdalin; neoplasms; alternative therapies; clinical trials

Received: 03 July 2017; Accepted: 15 July 2017; Published: 28 July 2017.
doi: 10.21037/amj.2017.07.16
View this article at: http://dx.doi.org/10.21037/amj.2017.07.16

Introduction and case presentation

A 48-year old Asian man presented to a tertiary care hospital emergency department with a two day history of black stools every two hours. He also reported one day of coffee ground emesis mixed with bright red blood. He had been feeling increasingly fatigued and dizzy. There was no history of non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulant, or alcohol use. His hemoglobin was measured to be 79 g/L.

His past medical history was significant for colorectal adenocarcinoma, with metastases to the liver, lung, and spine. He had undergone a laparoscopic left hemicolectomy and multiple bouts of chemotherapy which were complicated by a bowel obstruction and thrombocytopenia. Multiple metastatic lesions to the liver were treated with a right hepatectomy and computed tomography (CT)-guided radiofrequency ablation (RFA) to a remaining liver segment. Treatment failure of the RFA led to a trial of stereotactic body radiation therapy (SBRT) with good initial response. Despite these treatments, the patient developed bony thoracic lesions and recurrent, unresectable metastatic disease to his liver. Most recently, there were new left lung lesions suggestive of further metastatic disease.

The patient was not a surgical candidate, nor could he receive chemotherapy due to chronic thrombocytopenia. Consequently, the patient pursued complementary and alternative herbal treatments. His medications included:

(I) "Colorectal cancer" 1 tab daily;
(II) "Immune" 1 tab BID;
(III) "Low platelet" 3 tabs TID;
(IV) "Liver rescue" 3 tabs TID;
(V) "Vitamin B17" 1 tab TID.

On further questioning, the patient had been to Mexico two months prior to presentation pursuing alternative treatments where he purchased Vitamin B17 and had been taking this over the last four days.

An internet search revealed that the active component of B17 is Amygdalin (better known as Laetrile on the market). Amygdalin is formed from apricot kernels and

is metabolized by gut flora to glucose, benzaldehyde, and hydrogen cyanide.

Discussion

A brief history of amygdalin

Amygdalin was first discovered in the early 19th century in France as an active component of several fruit pits and raw nuts. Cyanide, one of the main metabolites of amygdalin, was thought to have anti-cancer properties and was introduced in the United States in the 1920's (1). Several formulations of Laetrile have been used over the years, including oral, intravenous, peritoneal, and intramuscular preparations. The oral formulation is far and above the most potent, related to the metabolic activity of gut bacteria (2).

There are several theories explaining how cyanide could specifically target cancer cells, while leaving non-cancer cells unharmed. It has been proposed that cancer cells exhibit higher beta-glucuronidase activity, thus making them more susceptible to the uptake and hydrolysis of amygdalin to cytotoxic cyanide (1). Another theory states that cancer develops as a result of specific vitamin deficiencies, and the addition of Vitamin B17 (Laetrile) can restore health to the body (1). Granted, these theories do have an experimental basis, however, the clinical evidence supporting the use of Laetrile as an anti-cancer agent is lacking.

Laetrile in clinical trials

Laetrile was considered to be an anti-cancer agent and had widespread use in the 1950's. Most formulations were produced in Mexico and marketed to North Americans with some scientific evidence at the time supporting its use.

A review published by Dorr and Paxinos in *Annals of Internal Medicine* in 1978 provided a comprehensive overview of the early studies on which Laetrile initially gained its popularity as a possible effective anti-cancer agent. Notably, these studies consisted of non-randomized, poorly controlled *in vitro* and animal studies. The most convincing data to support the use of Laetrile is derived from three Best Case Series published between 1953–1962 (3). However, it should be emphasized that none of these reports had adequate control groups and that many of the reported benefits of Laetrile were based on subjective improvements of quality of life (3). The authors of these original series did not mention placebo as a potential confounding variable (3). In addition to a lack of robust scientific evidence demonstrating efficacy, there were also multiple reports of cyanide toxicity-related adverse outcomes and deaths in patients who attempted Laetrile therapy (4).

As a result, the Food and Drug Administration (FDA) banned the use of Laetrile in the United States. More recently, a Cochrane Database review has published the following:

"The claims that laetrile or amygdalin have beneficial effects for cancer patients are not currently supported by sound clinical data. There is a considerable risk of serious adverse effects from cyanide poisoning after Laetrile or amygdalin, especially after oral ingestion. The risk-benefit balance of Laetrile or amygdalin as a treatment for cancer is therefore unambiguously negative" (5).

There have been no randomized controlled trials or quasi-RCTs to evaluate the effectiveness or safety of laetrile. Production and distribution of Laetrile has been banned in the United States, as supported by distinct public statements from organizations including the American Cancer Society and National Cancer Institute (1,6). In the 1970s, the mainstream nature of the controversy was such that even "Doonesbury", a popular syndicated daily comic strip, made reference to the dangers of Laetrile and how its ongoing availability and marketing is nothing more than a "money grab" (7). Despite this, Laetrile continues to be available in Mexico, marketed in products such as Vitamin B17 to a contemporary market of vulnerable and desperate consumers.

The importance of clinical trials

All new drugs and devices to be marketed in the United States and Canada are subjected to rigorous testing to demonstrate efficacy and safety. The U.S Food and Drug Administration and Health Canada have a mandate to provide the general population access to effective drugs while minimizing health risks associated with new products (8,9).

Animal studies to determine drug toxicity, followed by multiple levels of testing in Phase I–Phase III clinical trials is required before a new drug can reach the market and Phase IV post-marketing studies can still affect a products licensure.

In moving from bench to the "clinical trial bedside", multidisciplinary teams consisting of medical officers, statisticians, pharmacologists, pharmacokineticists, chemists, and microbiologists scrutinize all new drugs submitted to the FDA to determine if a drug can move on to the clinical trial phase (8). This process, although extremely time consuming and expensive, is what prevents a drug like Laetrile from being sold to local consumers.

Outcome of the case and conclusions

The patient introduced at the beginning of this report ultimately went on to have a gastroscopy which found multiple esophageal varices. These were most likely related to his metastatic liver disease and not a result of cyanide toxicity. His varices were banded and he recovered well in hospital and was discharged home. He was counseled on the dangerous consequences of using Vitamin B17 and was encouraged to discontinue use. He passed away in palliate care two months later.

Although there was no "medical climax" to this patient's presentation and course in hospital, this case brings about several key learning points we would like to highlight for medical trainees.

(I) The importance of taking a good history with medical curiosity: had it not been for a diligent junior resident who initially consulted on this case, the fact that this patient had the potential to be poisoning himself with cyanide, with no possible benefit, may not have been uncovered. It is crucial to take a detailed history and to clarify details by all means available—in this case, an internet search to look up a vitamin we are not taught about in medical school.

(II) Prescribing medications is not benign: it is important to remember that all drugs we prescribe for our patients come with a list of potential adverse effects and reactions. We should be thankful for the scrupulous process Health Canada and the FDA subjects all drugs to, however we must not forget that the human consuming the medication on the other side of the prescription pad is subject to both the benefits and consequences of taking a drug.

(III) Let us not forget the human element of our job. This case gives us a brief glimpse into the life of a man with a terminal, metastatic disease despite every imaginable curative effort. It is easy to forget about the emotional toll afflicted upon this man in the light of such an interesting case. Always take a moment to reflect on your day, to consider when you can take an extra moment at the bedside to show empathy or understanding, to counsel, or even to learn from our patients' stories and lives.

Acknowledgements

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Ai-Min Wu (Department of Spinal Surgery, Zhejiang Spinal Surgery Centre, Bone Research Institute, Orthopaedic Hospital & 2nd Hospital of Wenzhou Medical University, The Key Orthopaedic Laboratory of Zhejiang Province, Wenzhou, China).

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2017.07.16). EY serves as an unpaid board member of AME Medical Journal from Jun 2017 to Jun 2019. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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doi: 10.21037/amj.2017.07.16
Cite this article as: Nitikman M, Duncan K, Yoshida E. Metastatic colorectal cancer and Laetrile in the 21st century: persistence of a 1970s controversy. AME Med J 2017;2:100.

