

CASE REPORT

The Missing Trial Variable: A Case Report on Dietary Modification in a Patient with Durable Complete Remission After an Immunotherapy Clinical Trial for Metastatic Bladder Cancer

Linda L. Isaacs, MD; Nicholas J. Gonzalez, MD

ABSTRACT

A patient with metastatic bladder cancer has had an ongoing 9-year complete remission on a clinical trial of immunotherapy with nivolumab and ipimumab, but he also was following an intensive dietary and nutritional supplement regimen. Whether this combination or the

immunotherapy alone brought about his good outcome is unknown but could be clarified in future trials by improved data collection about dietary and supplement choices. (*Altern Ther Health Med.* [E-pub ahead of print.]

Linda L. Isaacs, MD, Private Practitioner, Austin, TX, USA.

Corresponding author: Linda L. Isaacs, MD

E-mail: lindaisaacsmid@hushmail.com

INTRODUCTION

Immunotherapy has transformed oncology, bringing about durable responses in diseases formerly resistant to treatment. But it does not always work, and it can have significant side effects. Both animal models and preliminary studies in humans suggest that dietary factors such as the Mediterranean diet, probiotics, and fiber may affect the outcome of treatment with immunotherapy agents, presumably through microbiome modification.¹⁻³ Diet and exercise choices have also been shown to improve disease-free and overall survival in patients with stage III colon cancer.⁴

However, formal assessments of diet and lifestyle choices are not usually part of clinical trial design. This case report describes a patient with metastatic bladder cancer who is a long-term survivor of a clinical trial of nivolumab plus ipilimumab but who also made substantial and continuing lifestyle changes.

CASE REPORT

The patient, who is now 79 years old, had a CT of the chest 2/2011 that showed enlarged mediastinal nodes, felt to be caused by a concurrent pneumonia; no biopsy was done. After an episode of hematuria, a bladder tumor was removed in 7/2012; pathology showed papillary transitional carcinoma, grade II/III, with no invasion of the lamina propria. He then began a nutritional program involving large doses of a pancreas product naturally rich in enzymes, an organic lacto-

ovo-vegetarian diet, and coffee enemas; further information on the components of this program has been published elsewhere.⁵⁻⁸ He was followed by serial cystoscopy.

He did well until 8/2014 when he developed a cough; a CT scan showed enlarged mediastinal nodes. A repeat scan on 9/2014 showed worsening of the adenopathy and development of pleural effusions. A PET scan in 11/2014 showed increased uptake in the mediastinal, hilar, and right retroclavicular areas. He underwent mediastinoscopy and lymph node biopsy; pathology showed metastatic carcinoma consistent with urothelial origin (positive GATA-3 staining and negative p63 and negative TTF-1 staining). Due to continuing dyspnea and cough, he received radiation to the mediastinum 2/2015. A CT scan one month after completing radiation showed improvement: "Confluent mediastinal lymphadenopathy is again noted, although slightly decreased in bulk ... Interval decrease in lymphangitic carcinomatosis evidenced by decreased bulk of confluent mediastinal lymphadenopathy and decrease in perilymphatic/peribronchovascular thickening throughout the lungs."

He then was admitted to a clinical trial, CheckMate 032, "A Phase 1/2, Open-label Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab in Subjects with Advanced or Metastatic Solid Tumors." He received both nivolumab and ipilimumab. On review of the trial admission history, no questions were asked about diet or lifestyle, nor did the consent form discuss data collection for diet or any other techniques that might be described as integrative. Pancreatic enzymes, a probiotic, and vitamin D were mentioned as medications in the visit notes from day 1 of his treatment.

His first dose of trial medication was on 4/2/2015. A scan on 5/13/2015 showed "No mediastinal or axillary lymphadenopathy. ... Interval increase in central,

peribronchial vascular consolidation with worsening fibrosis/traction bronchiectasis in most keeping with post-radiation changes.” His physician then noted on 5/14/15, “He has achieved a PR.” (PR = partial response) Subsequently, scans were essentially unchanged. He received his last dose of the study medication on 3/10/16. Follow-up scans were stable. In a note dated 11/17/2017, his physician commented on his “regimen of pancreatic enzymes and other supplements” and that he has “no evidence of disease on restaging scans.” A note on 5/7/19 after restaging scans once again showed no evidence of progression, stated, “he is now in a CR.” (CR = complete response) His most recent scan was 9/24/2021, again with no evidence of disease; he has also had multiple cystoscopies with no signs of disease. He continues to feel well, and, now, 9 years since he was admitted to the trial, he continues his nutritional regimen.

The formal results of the trial were published in 2019.⁹ There were two arms of the study where nivolumab and ipilimumab were administered together, with different doses of ipilimumab; objective response rates were 26.9% and 38.0% in those two arms. The median time to respond was 1.4 months, similar to the time in which this patient’s lymphadenopathy resolved. Median durations of response were 22.3 months and 22.9 months in the two combination treatment arms. Median overall survivals were 7.4 months and 15.3 months. Figure A3 from the article about the trial illustrates outcomes for the responders and their duration of response; of interest is the widely varying amount of time that responders spent on treatment. This patient received immunotherapy for less than a year; based on Figure A3, he is one of the few who discontinued treatment early.

DISCUSSION

It is difficult to know what has brought about this patient’s excellent outcome. Roughly 20% of patients in the Phase 1/2 study he took part in have had prolonged survival, but he discontinued treatment earlier than most. The lifestyle intervention he follows has multiple components, including an organic whole foods diet that is rich in fiber, possibly favorably affecting the microbiome. He has also been taking high dosages of a lyophilized pancreas product; pancreatic proenzymes in various preparations have been utilized for more than a century against cancer, with both case reports and basic science research supporting their use.⁷

While case reports such as this cannot conclusively establish anything, they can provide food for future thought and investigation. This particular case report could encourage clinical trial investigators to ask other long-term responders to immunotherapy what approach they took to diet, exercise, and other integrative techniques. If most or all long-term responders have been proactive about making lifestyle changes, finding this out could motivate researchers to collect data and institute research on these modalities.

Immunotherapy is an accepted treatment for metastatic urothelial cancer. However, in this particular trial, at most 38% of the patients had any response at all, and fewer had

long-term control or resolution of disease. If the diet, exercise, and nutritional supplement choices patients make are important for treatment outcomes, we need to know. Finding ways to help patients address these issues could help make treatment more universally effective.

PATIENT CONSENT

Consent of patient has been obtained and is available upon request

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