

Possible disease remission in patient with invasive bladder cancer with D-fraction regimen

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Abstract: Superficial bladder tumors are the most prevalent form of bladder cancers and transurethral resection is the primary surgical modality for those tumors. However, nearly 65% of patients will have tumor recurrence in five years while about 15% will have progression to muscle invasion. Thus, the primary therapeutic aim is to prevent multiple recurrences and progression to a more advanced, invasive disease. We here report an 87-year-old white male patient with invasive bladder cancer who received an unconventional oral regimen of D-fraction, the bioactive extract of Maitake mushroom (*Grifola frondosa*), following endoscopic transurethral resection of bladder tumor. Despite a high risk for disease recurrence, follow-up yet indicated no clinical evidence of progression of residual disease or recurrence of invasive cancer. It has been nearly two years but the patient remains remarkably well and appears to be in remission. To our knowledge, this is the first and only case report of possible disease remission in a bladder cancer patient after the two-year follow-up of D-fraction regimen, so that further studies with long terms are required for drawing a relevant conclusion. Nevertheless, it is conceivable that D-fraction is a natural agent that may have clinical implications in patients with superficial bladder tumors.

Keywords: invasive bladder cancer, D-fraction, disease remission

Introduction

Bladder cancer is the second most common urologic malignancy in the United States. Tumors fall into two categories: papillary lesions that tend to recur and invasive cancer. Although transurethral resection (TUR) is often performed as a primary therapy for papillary lesions, 50%–75% of patients will yet recur in five years and 10%–20% progress to invasive disease.¹ For invasive bladder cancer, radical cystectomy is the gold standard procedure.^{2,3} Several cytotoxic and immune modifying agents have been also used intravesically to treat bladder cancer. Intravesical administration of Bacillus Calmette-Guérin (BCG), an attenuated strain of *Mycobacterium bovis*, is the most effective immunotherapy for superficial bladder cancer and carcinoma *in situ* (CIS)⁴ among currently available therapeutic options. However, its benefits are sometimes outweighed by its severe side effects including cystitis, fever, allergic reactions, sepsis, and even death. These drawbacks thus limit its use in clinical practice, requesting a safer and more effective treatment modality with few side effects.

As an alternative approach, many natural agents/substances with low or negligible side effects have been gaining more attention for possible therapeutic modalities for various human malignancies. Although scientific studies have not been performed on most of them to demonstrate their biological and medicinal properties, some of them have been well characterized. For example, Maitake mushroom (*Grifola frondosa*) has been extensively studied for its potential medicinal properties and its immunomodulatory and antitumor activities have been thus far demonstrated in animals and humans.^{5,6} It is the fact that some cancer patients have been or are still taking a commercially available extract of this mushroom for therapeutic purpose.

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Case report

An 87-year-old retired OB-GYN physician, with a three-month history of intermittent hematuria, required emergent admission for painless gross hematuria in October, 2006 after failure to control the bleeding in an office cystoscopy. He had intermittent painless hematuria for six months prior to admission but had been lost to follow up. He also had an episode of urinary retention following a colon resection in 2002 but was not currently on alpha blocker therapy. In fact, he was on no medications at time of admission. The office cystoscopy revealed a large tumor on the right floor of his bladder, and satellite tumors surrounded this base appeared to be papillary tumors.

The patient was admitted and immediately underwent TUR of bladder tumor as he continued bleeding after the office cystoscopy. TUR showed multiple papillary and large ulcer base and the pathology report indicated he had invasive, transitional cell carcinoma (grade 3), T2b Nx Mx tumor. When he was discharged home three days after TUR, he was referred to a tertiary center to receive his follow-up care such as adjuvant chemotherapy, radical cystectomy, or external pelvic irradiation. He was also warned that he was likely have hematuria in the next six months unless he had surgery. However, the patient has refused all of these conventional treatments and started having an *unconventional* treatment using two supplements instead. One of the two supplements he took was a bioactive extract of Maitake mushroom, Maitake D-fraction® (Maitake Products, Inc., East Rutherford, NJ), following the recommended daily dosage, and the other was vitamin C (2,000 mg daily).

The patient has had no recurrent hematuria, pain, or urinary symptoms since then. In fact, office examination showed that his urine was clear with negative urine cytology, negative FISH (fluorescence *in situ* hybridization) test, and negative NMP-22 (nuclear matrix protein-22) test. It has been nearly two years but his condition yet remains exceptionally healthy.

Discussion

The natural history of bladder cancer is one of recurrence and progression, with recurrence most common in the first 12–24 months.⁷ Our patient was a high risk for disease recurrence, having multiple lesions with a large focus that was poorly differentiated carcinoma invading the deep muscle (ie, T2b Nx Mx). However, the only interventions our patient underwent were TUR of bladder tumor and adjuvant D-fraction regimen, because he refused radical cystectomy and other conventional interventions. Particularly, since

radical cystectomy is known as the gold standard procedure for such invasive cancer,^{1,2} performing TUR alone is unlikely to remove the whole tumor completely. The patient was then warned for disease recurrence unless appropriate post-TUR care was given to him. Yet, without any follow-up care, he had no recurrent hematuria with all negative results of cytology, FISH, and NMP-22 tests, which have exceptional sensitivity and specificity with a negative predictive value of 90.4%–98%.^{8,9} The patient indeed remains in good pathophysiological condition without any symptoms of his initial disease, indicating possible disease remission.

Maitake D-fraction is not just another mushroom extract found in the market but has been scientifically investigated for its potential medicinal effects/properties for the past 20 years. Besides its confirmed immunostimulatory activity, D-fraction was found to have antitumor activity in tumor-bearing mice, reducing cancer proliferation.⁶ An early nonrandomized clinical study on patients with various cancers also showed certain improvements in those cancer patients.¹⁰ In addition, D-fraction was capable of inducing apoptosis (programmed cell death) in human prostate cancer cells¹¹ as well as >90% growth reduction in human bladder cancer cells.¹² Thus, these studies support the notion that D-fraction has potent anticancer activity on animal and human malignancies.

Above all, the most important issue of D-fraction would be its safety. It is supported by the fact that the US Food and Drug Administration (FDA) had exempted D-fraction from a Phase I toxicology study. The FDA also approved D-fraction for an Investigational New Drug (IND) application to conduct a Phase II pilot study on patients with advanced prostate and breast cancer, further granting its use in human cases.¹³

This case study describes an invasive bladder cancer patient at a high risk for disease recurrence who only followed a D-fraction regimen (with vitamin C) refusing other medical interventions. The two-year follow-up yet indicated no clinical evidence of progression of residual disease or recurrence with possible disease remission. However, we are recommending him to have additional viable options such as cystoscopy, computed tomography scan, or another TUR for further assessment and confirmation of his latest disease status. In addition, a correlation between cancer suppression and D-fraction needs to be fully established and also this is only one case with merely two-year follow-up, thereby requiring more case studies with long terms to draw any affirmative conclusions. Meanwhile, it is yet plausible that D-fraction is a natural, safe, and promising agent that may have clinical implications in patients with superficial bladder cancer.

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