ORIGINAL RESEARCH

# Complete Remission of BCG-Refractory High-grade Bladder CIS with Pharmacologic Ascorbate and Mistletoe

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## ABSTRACT

**Context** • Bladder cancer is the fourth-most-common cancer in males in the U.S., who develop about 90% of the high-grade, carcinoma in situ (CIS) of non-muscle involved disease (NMIBC). Smoking and occupational carcinogens are well-known causes. For females without known risk factors, bladder cancer can be regarded as a sentinel environmental cancer. It's also one of the costliest to treat due to its high rate of recurrence. No treatment innovations have occurred in nearly two decades; intravesical instillation of Bacillus Calmette-Guerin (BCG), an agent in short supply globally, or Mitomycin-C (MIT-C) is effective in about 60% of cases. Cases refractory to BCG and MIT-C often undergo cystectomy, a procedure with numerous impacts on life styles and potential complications. The recent completion of a small Phase I trial of mistletoe in cancer patients that have exhausted known treatments at Johns Hopkins provides corroboration of its safety, with 25 % showing no disease progression.

**Objective** • The study examined the benefits of pharmacologic ascorbate (PA) and mistletoe for a nonsmoking female patient with an environmental history of NMIBC refractory to BCG, in a non-smoking female with exposures in childhood and early adult life to several known carcinogens, including ultrafine particulate air pollution, benzene, toluene, and other organic solvents, aromatic amines and engine exhausts, and possibly arsenic in water.

**Design** • The research team performed an integrative oncology case study on pharmacologic ascorbate (PA) and mistletoe, both agents shown to activate NK cells, enhance growth and maturation of T-cells, and induce dose-dependent pro-apoptotic cell death, suggesting shared and potentially synergistic mechanisms.

**Setting** • The study began at the University of Ottawa Medical Center in Canada with treatment continuing over six years at St. Johns Hospital Center in Jackson, Wyoming, and George Washington University Medical Center for Integrative Medicine, with surgical, cytological, and pathological evaluations at University of California San Francisco Medical Center.

**Participant** • The patient in the case study was a 76-year-old, well-nourished, athletic, nonsmoking female with high-grade CIS of the bladder. Her cancer was considered to be a sentinel environmental cancer.

**Intervention** • Intravenous pharmacologic ascorbate (PA) and subcutaneous mistletoe (three times weekly) and intravenous and intravesical mistletoe (once weekly) were employed for an 8-week induction treatment, using a dose-escalation protocol as detailed below. Maintenance therapy was carried out with the same protocol for three weeks every three months for two years.

**Results** • The patient has experienced a cancer-free outcome following 78 months of treatments that incorporated intravesical, intravenous, and subcutaneous mistletoe; intravenous PA; a program of selected nutraceuticals; exercise; and other supplementary treatments.

**Conclusions** • This study is the first reported instance of combined treatments to achieve complete remission for high-grade NMIBC refractory to BCG and MIT-C, using intravesical, subcutaneous, and intravenous mistletoe and intravenous PA. It includes pharmacological information on possible mechanisms. In light of the global shortage of BCG, the high proportion of cases refractory to BCG and MIT-C, the unproven use of costly off-label pharmaceuticals, such as gemcitabine, and the relative cost-effectiveness of mistletoe and PA, clinicians should give serious consideration to employing these combined functional medicine treatments for BCG- and MIT-C-refractory NMIBC. Further research is needed with additional patients that can advance our understanding, including standardization of methods for systematically evaluating combined therapies—blinded and non-blinded, nomenclature regarding mistletoe preparation, doses, concentrations, regimes of administration, lengths of treatment, targeted cancer types, and other aspects. (*Altern Ther Health Med.* 2023;29(4):6-17).


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Globally, bladder cancer is the sixth most common in men and the seventeenth most frequent in women. In the U.S. it is the fourth most common cancer in menThe World Health Organization estimates that almost 550 000 new cases occurred in 2018.[1] The National Comprehensive Cancer Network indicated that in the USA in 2019, 17 670 deaths with 80 470 new cases of the disease occurred.[2] In China, approximately 200 000 cases are estimated to occur annually.[3] About 90% of all bladder cancer is non-muscle involved (NMIBC) and affects men,[4] and the overall rate of recurrence is 60% to 70%.[5] No major innovations in treatment have been developed in nearly two decades.[6]

Known risk factors include smoking, pelvic radiation, workplace exposures to aromatic amines, organic solvents, chronic phenacetin use or infection, family history, diabetes, obesity, and some pharmaceuticals. Men are about three to four times more likely than women to get bladder cancer, but women typically are first diagnosed with more-advanced disease with worse prognoses.[7]

Due to its high rate of recurrence and low mortality, bladder cancer is among the most costly malignancies to treat, based on lifetime cumulative expenses per patient for surveillance, high rates of recurrence, surgical monitoring and surveillance, and treatments.[8] Because bladder cancer is relatively infrequent in women, when it occurs in those with no known risk factors, such as smoking, family history, or obesity, the disease can be considered to be a sentinel environmental cancer.

**Intravesical Therapy**

Medical historians note that the first recorded treatments placing material into the bladder originated in the eleventh century, when the Persian physician Avicenna described using a hollow reed to insert different agents through the urethra to treat bladder dysfunctions.[9] From the Middle Ages through to the mid-twentieth century, toxic materials ranging from acidic solutions of mercury to iodine, radioisotopes, and precursors of poison gas had been injected into the bladder, with unpredictable outcomes including disfiguration and death.[10]

Contemporary diagnosis is confirmed through transurethral bladder resection (TURB). Most disease, more than 90%, originates within the urinary bladder, with 8% in the renal pelvis and 2% in the urethra or ureter.[2]

Blue-light cystoscopy (BLC) can identify malignant cells after applying the photosensitizing agent hexyl-aminolevulinate (HAL) into the urothelial cytoplasm, where it undergoes metabolism. Normal cells excrete HAL, so it doesn't accumulate. In contrast, malignant cells lack certain heme-metabolizing enzymes, and when exposed to blue light, they fluoresce red due to photoactive porphyrins. BLC can identify multifocal tumors or carcinoma in situ (CIS) that are subsequently confirmed by pathological analysis.[2]

Clinically three broad stages of bladder cancer have been identified: NMIBC, either papillary or epithelial; muscle-invasive disease; and metastatic disease. Bladder preservation can be maintained when patients have early stage NMIBC that responds favorably to therapy. For muscle-involved disease, or for NMIBC that is high grade, cystectomy is often appropriate, if other comorbidities don't preclude that complex surgery. For advanced metastases, extending survival and improving quality of life (QoL) are the major goals.[2]

**Intravesical BCG as NMIBC treatment**

Modern treatments for bladder cancer derived from the observations of the prolific statistician Raymond Pearl, who reported in 1929 that those who died from tuberculosis didn't have cancer.[11] Subsequent experiments have shown that Bacillus Calmette-Geurin (BCG) could suppress tumors in rodents that had been injected with various cancer cells.[12]

Half a century ago, when most bladder cancer treatments were ineffective, an enterprising Canadian physician reported that eight out of nine patients in a case series, who received an attenuated form of the tuberculosis bacterium directly into their bladders, were clear of disease.[13] Currently, the (SWOG) Protocol of induction and maintenance, with 6 weeks of intravesical treatments with BCG, comprises the standard protocol, with TURB evaluation at one month after treatment ends. Where tumors have receded, that treatment is followed by repeated maintenance treatments for 3 consecutive weeks every 3 months for a period of 2 years.[2]

After more than forty years of successful experience using BCG, theoreticians propose that BCG recruits cells from the bladder's lining—both cancerous and normal—to destroy malignant growths by ramping up natural killer (NK) cells[14] and by secreting tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)[15] that preferentially block and kill malignant cells. Systemic, nonspecific, immunostimulatory responses increase pro-inflammatory cytokines producing pyrexia and flu-like symptoms that can last 48 to 72 hours and mimic bladder infections.[2]

While BCG has protective effects against the specific diseases for which it was designed, it also has provided a useful treatment for more than half of all cases of NMIBC for more than half a century. Consistent with the SWOG protocol, intravesical instillations of six weekly sessions with standard doses of BCG provide effective therapy for about 60-70% of all cases.[2]

When patients are refractory to BCG, other off-label intravesical chemotherapy agents are employed, including gemcitabine, interferon alpha, and Mitomycin-C (MIT-C). For patients who don't respond to those or other off-label treatments and for those with either high-grade disease or muscle-involved disease, cystectomy is in order, together with prostatectomy or complete hysterectomy. With high rates of complications—about 50%—many, especially elderly patients or those with comorbidities, refuse to undergo cystectomy.

**Current Case Study**

The current study intended to examine the benefits of pharmacologic ascorbate (PA) and mistletoe for a nonsmoking female with an environmental history of NMIBC refractory to BCG, with exposures in childhood and early adult life to several known carcinogens, including ultrafine particulate air pollution,

benzene, toluene, and other organic solvents, aromatic amines and engine exhausts, and possibly arsenic in water.

The research team performed an integrative oncology case report on pharmacologic ascorbate (PA) and mistletoe, both agents shown to activate NK cells, enhance growth and maturation of T-cells, and induce dose-dependent pro-apoptotic cell death, suggesting shared and potentially synergistic mechanisms. The study began at the University of Ottawa Medical Center, Department of Urological Oncology in Canada with treatment continuing over six years at St. Johns Hospital Center in Jackson, Wyoming, and George Washington University Medical Center for Integrative Medicine.

## CASE STUDY AND ENVIRONMENTAL HISTORY

For a single case report in accordance with the operating rules for George Washington University Medical Center and our other organizations, institutional review approval wasn't required. Moreover, the individual in the case study gave both written and verbal consent for this case to be presented.

**Patient's case history.** Born in 1946, the patient in the case study was a 76-year-old, well-nourished, athletic, nonsmoking female, 67.5 inches tall and weighing 133 pounds, with high-grade CIS of the bladder. In early childhood, she resided in the Monongahela Valley, Pennsylvania, which was a center of steelmaking and coke-oven and zinc refining (Table 1). Levels of particulate and gaseous air pollution produced a lethal smog in Donora in 1948, resulting in 20 deaths in 5 days.[16]

Her father had been a machinist, who washed her hands and his with gasoline. He developed the occupational cancer multiple myeloma at age 53. Her youth involved playing on a nearby dump, where slag containing heavy metals from the blast furnace was deposited.

In addition, at a time when few swimmable pools existed, her family often swam in a brown water lake that had water that had been used to remove coal impurities, resulting in coal slurry stored with coal ash.

In high school and college and in a postdoctoral fellowship at age 34 during laboratory classes in molecular biochemistry and immunology, she worked with phenols and other laboratory chemicals without gloves, fume hoods, respirators, or other protective personal equipment.

With no known risk factors for this typically male cancer and given her history of exposure to several known environmental carcinogens, her bladder cancer was considered to be a sentinel environmental cancer. Her comorbidities included Hashimoto's thyroiditis, moderate hypertension, and autoimmune gastritis.

**Medical history.** Following hematuria, the patient first presented in 2013 with benign neoplasia with a low malignancy potential (BNLMP), confirmed by TURB. Table 2 provides the timeline of diagnosis and treatment for the case study. The patient underwent cystoscopic surveillance every six months. In June 2016, high-grade CIS was confirmed by BLC and TURB. Immediately postoperatively, 40 mg of intravesical MIT-C in 20 cc of water was administered, because no bladder perforation or sign of infection had occurred.

Four weeks later, the patient began induction of weekly BCG following the SWOG protocol, at 40-mg doses in 10 cc

**Table 1.** Timeline of Relevant Environmental Exposures for Bladder Cancer in Nonsmoking Female, Born 1946

| Date | Incident | Chemicals |
|---|---|---|
| 1948 | Killer-smog survivor from Donora, PA; ultrafine particulates | Zinc refinery, coke and coal smoke |
| 1950-1953 | Handwashing | Gasoline—benzene, toluene, and other aromatic hydrocarbons; kerosene |
| 1948-1956 | Playground on slag dump | Cadmium, lead, other heavy metals |
| 1950-1956 | Swimming | Coal mine lake |
| 1956-1960 | Play with homemade rocket fuel; backyard chemistry experiments | Nitrogen oxides, phenol |
| 1963-1966 | Work as a laboratory technician | Phenols |
| 1982-1983 | Postdoctoral laboratory immunology | Chloroform, phenols, acrylamide |

**Table 2.** Timeline of Diagnosis and Treatment

| Date | Diagnosis | Treatment |
|---|---|---|
| 2012-2015 | Benign neoplasia with low malignancy potential, confirmed by TURB | Routine cystoscopic surveillance, 2x/year |
| June 2016 | High-grade carcinoma in situ, with no muscle involvement, confirmed by TURB | One postoperative treatment: Intravesical dose of 40 mg of mitomycin in 20 ml of sterile water |
| July-August 2016 | | Induction treatment: Six weeks of 81 mg of BCG, with maintenance at three-month intervals, following Southwest Oncology Protocol |
| June 2017 | High-grade carcinoma in situ, with no muscle involvement, confirmed by TURB | Induction with integrative multi-modal protocol (Table 3A) |
| July-August 2017 | | Integrative, multimodal protocol maintenance (Table 3B) |
| September 2017 | No sign of tumor, confirmed by TURB | |
| November 2017-November 2019 | | Maintenance protocol once monthly treatments (Table 3B) |
| 2017-2022 | | Cystoscopic and cytologic monitoring every 3 months with no evidence of bladder disease, confirmed by TURB |

**Abbreviations:** BCG , Bacillus Calmette-Guerin; TURB, transurethral bladder resection.

**Table 3.** Combined Intravenous and Intravesical, Integrative Induction Protocol for Treatment of High-Grade Carcinoma in Situ of the Bladder, for 8 weeks

| **3A. Integrative Multimodal Protocol for Eight Weeks** | | | |
|---|---|---|---|
| **Once weekly** | **Three times per week** | **Once weekly** | **Twice weekly** |
| Escalating doses of intravesical mistletoe mali, at 400, 800, 1200, 1600, and 2000 mg, retained for 2 hours | Alternating days: Subcutaneous doses of 50 mg of mistletoe and 50 mg of abietis | Intravenous mistletoe mali, escalating up to 1200 mg, in 100 cc increases | Intravenous vitamin C: 75 grams in 750 ml of sterile water with 4 mL Mg; 3 mL K 50 mg each of Zn, Cr,, Se; and one gram of B-12, infused over 1.5 hours and protected from light |
| **3B. Integrative Multimodal Maintenance Protocol** | | | |
| **November 2017 to November 2020—For 3 Weeks Every 3 Months** | | | **November 2019—Present Maintenance** |
| **Weekly** | **Three times per week** | **Twice weekly** | **Monthly** |
| 1200 mg of intravesical mistletoe *mali* | 40 mg of subcutaneous mistletoe*pini* | Intravenous ascorbate at 25 gms in 250 mL sterilewater, 2mL K, 1 mg K | 600mg of intravenous mistletoe *mali;* 50 grams of intravenous ascorbate |

**Table 4.** Induction Nutraceuticals

| Period | | | |
|---|---|---|---|
| Daily | 1804 mg of Curcuma longa rhizome (EuroMedica,Green Bay, WI, USA) | 5000 IU of Vitamin D (Pure, Sudbury, MA , USA) | Omega-3 BID—borage seed, flax seed, and deep-sea fish oil; DHA, ALA, EPA, GLA; organics |
| | 200 mg of ubiquinone Co-Q 10 (L Apothecary Suffield, Connecticut, USA) | 20 mg of melatonin at night qd, started at 3 mg and slowly increased until target dose of 20 mg reached (Pure) | One gm BID inonotus (Chaga) |
| | Obliquus (Host Defense, Olympia WA , USA):<br>• One gram BID Stamets 7 Royal<br>• 214 mg of Sun Blazei (Agaricus brasiliensis f. blazei) mycelium<br>• 214 mg of Cordyceps (Cordyceps militaris) mycelium<br>• 214 mg of Reishi (Ganoderma lucidum s.l.) mycelium<br>• 214 mg of Maitake (Grifola frondosa) mycelium<br>• 214 mg of Lion's Mane (Hericium erinaceus) mycelium<br>• 214 mg of Chaga (Inonotus obliquus) mycelium<br>• 214 mg of Mesima (Phellinus linteus) mycelium | | |
| During Induction | Probiotics: 50 billion, 12 different strains (Renew Life Extra Care, Durham, NC , USA) | | |
| During Maintenance | • 20 billion CFU of live bacteria from 14 probiotic strains (Megafood Fort Lauderdale, FL, USA)<br>• 10 mg qd of melatonin (Pure)<br>• 4 grams of FiberSmart, made with flaxseed, probiotics and L-glutamine (Renew Life, Durham, NC , USA) | | |

**Abbreviations:** ALA, alpha lipoic acid; DHA, dehydroascorbate acid; EPA, eicosapentaenoic acid; GLA, gamma-linolenic acid

of saline for 6 weeks. TURB was repeated at one month after induction ended in August 2016, and the patient showed no regression of CIS, with spread to the trigone and dome. For patients refractory to BCG and MIT-C, repeated BCG has a 20% success rate, and cystectomy is often undertaken as advancement of the disease is likely.

**Integrative treatments.** Based on a literature review indicating the relevant properties of medicinal forms of mistletoe and the research team's discussions, an integrative course of treatment was devised employing intravesical, intravenous, and subcutaneous mistletoe; intravenous PA; and other integrative therapies. Earlier studies had suggested the value of treatments for NMIBC refractory to BCG that combined weekly treatments of a one-third dose of BCG, 27 mg, plus 50-million units of interferon-alpha 2B (interferon-α2B).[17]

In September 2016, the research team employed a dose-escalating protocol of intravesical instillation of mali mistletoe. A phase Ib/IIa trial using mistletoe employment of escalating intravesical doses of up to 675 mg of *mali,* with no serious side effects, and no dose-limiting toxicity.[18]

As salvage treatment after the patient's high-grade disease became refractory to BCG, an eight-week induction protocol (Table 3A) was developed that included: (1) weekly administration of BCG/3, with 50-million units interferon-α2B; (2) at week two on alternate days, a combination of those treatments using a weekly dose-escalating protocol of intravesical *mali* mistletoe, at 200 mg, 400 mg, 800 mg, 1200 mg, 1600 mg, and 2000 mg, added to 10 cc of saline, with no toxicity; (3) twice weekly, 75 gms of intravenous PA, (750 ml sterile water, 4mL Magnesium, 3mL Potassium, and (4) subcutaneous administration of *abietis* mistletoe, administered 3 times a week on days when the IV administration didn't occur. The TURB with BLC and pathology, conducted at 4 weeks after the 2016 induction had ended, found no sign of disease.

In an adaptation of the SWOG, maintenance treatments were begun at 3 months after induction ended for 3 consecutive weeks with *mali* intravesical and subcutaneous *pini* mistletoe, and intravenous PA. No additional BCG/3 or interferon-α2B was included. Table 3B shows that the treatments consisted: (1) of 50 gmof intravenous PA (2) of

intravesical mistletoe *mali,* at 700, 1400, and 2400 mg; (3) of intravenous mistletoe *mali,* at 400 mg, 500 mg, and 600 mg—the dose of mistletoe was established that induced moderate pyrexia; (4) of subcutaneous mistletoe *pini* at 20 mg and 50 mg, and (5) of nutraceutical adjuncts.

In addition, a lifelong program of hatha yoga, acupuncture, mindfulness meditation, chiropractic treatments, massage, and intense cardiovascularactivities , 4-8 hours weekly, was continued. After 12 and 24 months of maintenance treatment, the TURB with BLC confirmed that no sign of the disease existed in 2018, a condition that had continued as of December 2022.

Monthly maintenance was undertaken thereafter, including: (1) a single administration of 50 gm of PA intravenously, (2) 600 gm of intravenous mistletoe mali, (3) subcutaneous mistletoe *pini* at 50 mg 3 times in one week per month, and (5) nutraceuticals and other support (Table 4).

Some 77 months after the integrative combined treatment was begun, after six TURBs, 12 cystoscopies, and 24 intravesical treatments over the prior 6 years, the patient's bladder epithelium currently appears unremarkable. The pathology and cytology testing as of May 2022 confirmed no sign of high-grade CIS, originally detected in June 2016.

## DISCUSSION

### Diagnosis of Sentinel Environmental Cancer

Overall, about one in 10 new cases of bladder cancer are associated with workplace carcinogens, and one to 2 in 10 cases of the disease occurs in females.[19] High risks have been detected for those working with aluminum, metal, aromatic amines, polycyclic aromatic hydrocarbons, oil, leather, dye, and paint.[19] Few studies of occupational or environmental cancer causes have included women, so it's challenging to apportion those causes' roles in the disease.[20] One large, population-based, case-control study found that women using permanent hair dyes faced a significantly elevated risk of developing bladder cancer.[21] Those who were slow acetylators—the *N*-acetyltransferase (NAT)-2 slow acetylation phenotype—were at the highest risk.

It's noteworthy that the patient in the current case study didn't dye her hair and didn't work regularly in any of the known occupational risk groups, nor was she a smoker. All of these considerations strengthen the argument to conclude that her disease can be regarded as a sentinel environmental bladder cancer.

### Mistletoe Treatment

For a century in Germany and Switzerland, a number of forms of mistletoe have been synthesized and extracted for medical purposes, including the reduction of side effects of chemotherapy; salvage therapy for breast, colon, and lung cancer; and support for metastatic disease. Mistletoe grows opportunistically by latching onto the bark of various trees and budding on the barks of both deciduous and evergreen trees. The scientific name for mistletoe, *Phoradendron*, means thief of the tree.

While more than 1000 species of mistletoe exist, the anticancer properties identified thus far are chiefly from European variants of *viscum album* that occur on apple (*mali*), pine (*pini*), fir (*abietis*), oak (*quercus*), hawthorn (*crataegus*), ash (*fraxini*), elm (*ulmi*), and poplar (*populi*). Currently, the four main European mistletoe producers rely on mistletoe grown in France, Switzerland and Germany and include: (1) Iscador (Arlesheim, Switzerland), from 5 host trees[22]; (2), Helixor Heilmittel GmbH in Rosenfeld, Germany), from 3 host trees[23]; (3) Iscucin (Abnoba, Wala in Eckwälden/Bad Boll, Germany), from 8 host trees[24]; and (4) Abnoba Viscum (Abnoba), Niefern-Oeschelbronn, Germany, from 5 host trees.[25] These preparations differ with respect to their extraction processes, such as aqueous fermentation, water extraction, and pressing, and to the proportion of relevant ingredients, particularly mistletoe lectins, vincetoxins, and polysaccharides.

Reviews of mistletoe illustrate the challenges of the synthesis of systematic evidence for complex interventions. In 2008, a systematic Cochrane Review of all reported forms of mistletoe, as either an adjunct or a primary cancer treatment, excluded 80% of all studies that had been conducted.[26] Those 16 out of 80 studies that met the criteria for inclusion provided some evidence that mistletoe can increase both the length and quality of patients' lives, especially in cases involving metastases.[27]

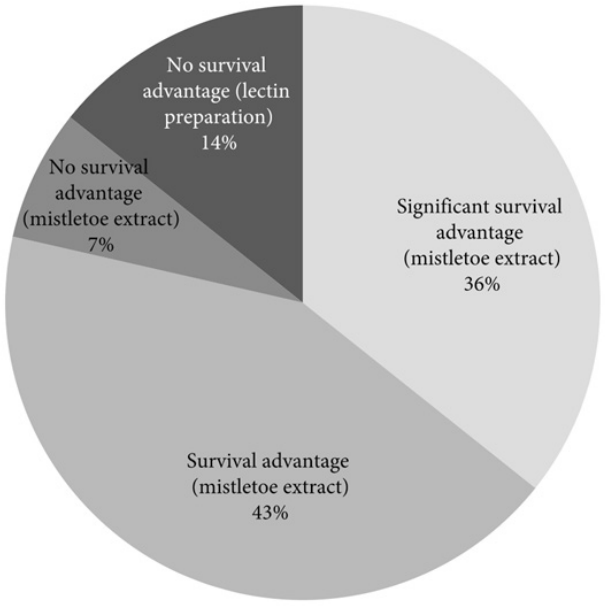
One systematic review of randomized controlled studies (RCTs), found no overall evidence of efficacy for mistletoe in cancer treatment nor advances in QoL.[28] A contrary view has been taken by European experts who reported that the majority of clinical studies show evidence of the efficacy of mistletoe,[28] with few major side effects.[29] Not including the methodology and conclusions of Freuding et al,[28] note that most clinical reports of mistletoe treatments included in that review involved multimodal treatments that were excluded without providing criteria for their exclusion.

Figure 1 from Matthes et alanalysis of survival in clinical studies of mistletoe indicated that nearly 80% showed significant benefits.[27] An additional systematic meta-analysis of all non-blinded applications found overall efficacy for viscum album in improving QoL in cancer treatment and increasing survival, while acknowledging the methodological challenges of interpreting such information.

In addition to clinical reports on a wide range of cancers, in-vitro and in-vivo evidence provides instructive information, particularly with respect to timing and route of exposure of various forms of mistletoe for the treatment of bladder cancer. Thus, a review of 37 relevant experimental studies on mistletoe concluded that while the majority showed evidence of anticancer effects, the lack of standardization as to extraction and nomenclature precluded definitive conclusions.[30]

With respect to bladder cancer, those reviewers noted that potent antitumor effects occurred in an experimental study that had reported significant reductions in induced disease in a rat model following direct intravesical instillation

**Figure 1.** Survival Advantage in Reports of Mistletoe in Clinical Use[27]




of mistletoe lectin into the bladder.[31] Similar results with intravesical treatments were reported within 4 weeks by Mengs et al in mice implanted with urinary bladder carcinoma MB49 cells, which found dose-dependent, statistically significant, tumor growth inhibition in treated groups.[32]

More recent advances in the use of mistletoe over the past decade have been reported for treatment of several metastatic cancers, including gastric, pancreatic, prostate, non-small cell lung, glioma, and cervical cancers.[33] Major improvements in survival and in QoL have also been recently reported in a meta-analysis that included both RCTs and nonrandomized studies of adjuvant subcutaneous mistletoe versus standard treatment with oral etoposide for osteosarcoma patients after a second relapse.[34] It's noteworthy that in relapsed osteosarcoma, the rate of five-year disease-free survival (PRDFS) after the second relapse is typically less than 20 percent. In contrast to that poor prognosis, this small RCT study with a median follow-up time of 83 months, reported a median of disease-free survival (PRDFS) of 106 months in the Viscum-treated group in the five of the nine patients who never relapsed.[34] In comparison, the median PRDFS was only 7 months in the etoposide group, where all patients relapsed (hazard ratio HR 0.287, 95% KI: 0.076-0.884, $P = .03$). Thus, some 12 years from the start of the study, mistletoe treatment provided significantly more disease-free survival for half of all patients, contrasting with the 7 months of average survival in the conventionally treated group. In addition, the cost-effectiveness of the mistletoe treatment for stage IV non-small cell lung cancer has recently been supported by German integrative oncology physicians in a cross-sectional observational study.[35] Such encouraging results were obtained during the course of a RCT employing viscum album extract with metastatic pancreatic cancer that the independent reviewers of the study decided to provide mistletoe to all the remaining patients in the trial deeming it 'medically unethical' not to offer that treatment given the poor prognosis and QoL.

The National Cancer Institute provides a summary of other in-vitro and in-vivo results with mistletoe as well.[26] A robust meta-analysis of RCTs demonstrated that mistletoe reduced fatigue in cancer patients at a level comparable to that induced by regular exercise.[36]

For the past fifty years, more than a thousand in-vitro and in-vivo experiments of varying scientific quality and rigor have shown that major components of various forms of mistletoe can be especially potent against malignancies. A recent study found that mice with induced glioblastoma multiforme (GBM) responded favorably to a combination of radiochemotherapy and mistletoe with enhanced t-cell targeting of gliomas.[37]

In 2006, the *British Medical Journal* reported that about $60 million was estimated to be expended on refined extracts of mistletoe each year in continental Europe, with insurance covering many of these applications.[38] In the USA and Canada, growing numbers of clinicians are relying on several varieties of mistletoe as well.[39] Clinicaltrials.gov lists more than 15 different trials underway[38] that are employing mistletoe for a variety of metastatic cancers, including non-small cell lung cancer, pancreatic cancer, gastric cancer, and others; these studies have recruited cancer patients for whom conventional treatments have failed.[39,40] In German-speaking countries nearly nine out of every 10 oncology patients employ mistletoe as part of their treatment.[27]

Currently mistletoe is being administered clinically for diseases refractory to conventional treatments by some functional-medicine practitioners at several major university centers, including George Washington University, the Center for Integrative Medicine, Thomas Jefferson University, the Karolinska Institute, and the Ottawa Center for Integrative Oncology. Johns Hopkins University Medical Center has completed a Phase I trial in the USA for stage IV cancer patients that have exhausted all known treatments, reporting no serious toxicity, some stabilization of disease in 25% of the 21 participants and some indication of tumor regression that did not reach statistical significance. Other studies can be found on clinicaltrials.gov. More than 500 physicians have undergone training in the use of mistletoe for cancer treatment in the past three years.

A European trial for intravesical mistletoe for NMIBC, low-grade, bladder neoplasms is underway, headed by Abnoba, a firm producing the drug. This randomized, open-label, active-controlled, prospective, multinational Phase III confirmative study of intravesical mistletoe compares the safety and toxicity of two treatment arms, one using mistletoe from Abnoba, Mali VISCUM 900, and one using Mitomycin C (MIT-C ) It employs an adaptive design and includes patients with superficial bladder carcinoma, with an evaluation of the time to tumor recurrence. A further objective is to measure treatment efficacy by calculating prognosis for recurrence and progression after one year, tumor grading in case of a recurrence, and QoL.

Regarding possible mechanisms of action, experimental studies indicate that refined mistletoe extracts can directly stimulate NK cytotoxicity *in vitro* as well as indirectly in a cytokine-like manner.[41,42] Mistletoe lectins have been identified as active components and exhibit cytotoxic effects as well as immunomodulatory activity. It appears that one key anticarcinogenic component may be polysaccharide carbohydrates rather than lectins. Clinical application of mistletoe extracts or isolated lectins has been found to augment both number and activity of NK cells in peripheral blood in a dose-dependent manner.[43] Patients in that study undergoing surgery for colorectal cancer who received a mistletoe infusion had less suppression of NK cells than those that didn't receive a perioperative infusion. As with all therapeutic agents, nonresponders also have been described.

The extensive, predominantly European literature that exists on mistletoe use in oncology can't be adequately reviewed in this paper. Without a doubt, a great deal of methodological heterogeneity exists among the studies. Different forms of mistletoe are employed as well as different routes of exposure in both experimental and clinical studies. The fact that most studies aren't randomized or blinded limits the inferences that can be drawn about efficacy.

Accordingly, the current research team concurs that that a need exists for clear, consistent reporting guidelines regarding in-vivo and clinical mistletoe experiments for cancer treatment, including standardization of mistletoe preparation and delivery.[31] Among the relevant mechanisms that have been proposed are a variety of anticarcinogenic properties, including cytotoxicity of macrophages and phagocytosis by immune cells through increased tumor necrosis factor alpha (TNFα), interleukin-1 (IL-1), IL-2, and IL-6 cytokine secretion.

**Pharmacologic Ascorbate**

Under the circumstances of a patient's cancer being refractory to BCG and MIT-C, consideration has been given to including the use of pharmacologic ascorbate (PA), as evidenced by the growing number of experimental and clinical applications of this therapy in oncology and the indications of its success in combination with other therapies.[41] In Rees et al's study, the patient was negative for glucose-6-phosphate dehydrogenase deficiency (G6PD), an X-linked recessive metabolic disorder that predisposes individuals to hemolytic anemia and jaundice and that can be triggered by exposure to intravenous PA.[44] That study's therapy employed a dose-escalating approach, increasing from 25, 50, to 75 grams in the first 3 week. Throughout the remaining 5 weeks of the induction period, 75-gram infusions were administered twice weekly.

Early studies that purported to investigate and reject the utility of PA in the treatment of cancer have been found to have been methodologically flawed, because they failed to appreciate the central role of the route of administration.[45] It's now understood that oral dosing, used in early trials of vitamin C, can't achieve pharmacologically relevant serum levels, and clinical experience and experimental research have determined that the dose and route of exposure are pivotal determinants of efficacy.[40] Higher pharmacologic concentrations and greater cytotoxic impacts on cancer cells are only achieved with IV PA as compared to oral dosing, and it's postulated to generate free radical damage to aberrant cells.[46] Intravenous administration achieves the high plasma concentrations not achievable through oral administration.[47-50]

Detailed clinical investigations at the National Institutes of Health and elsewhere have demonstrated that due to tight physiological control of ascorbate absorption and excretion, intravenous and oral administration of ascorbate yield profoundly different plasma concentrations. When given orally, fasting plasma concentrations remain below 100 µM.[46] Moreover, when doses exceed 200 mg, the absorbed dose and bioavailability decreases, while renal excretion increases.[46,51]

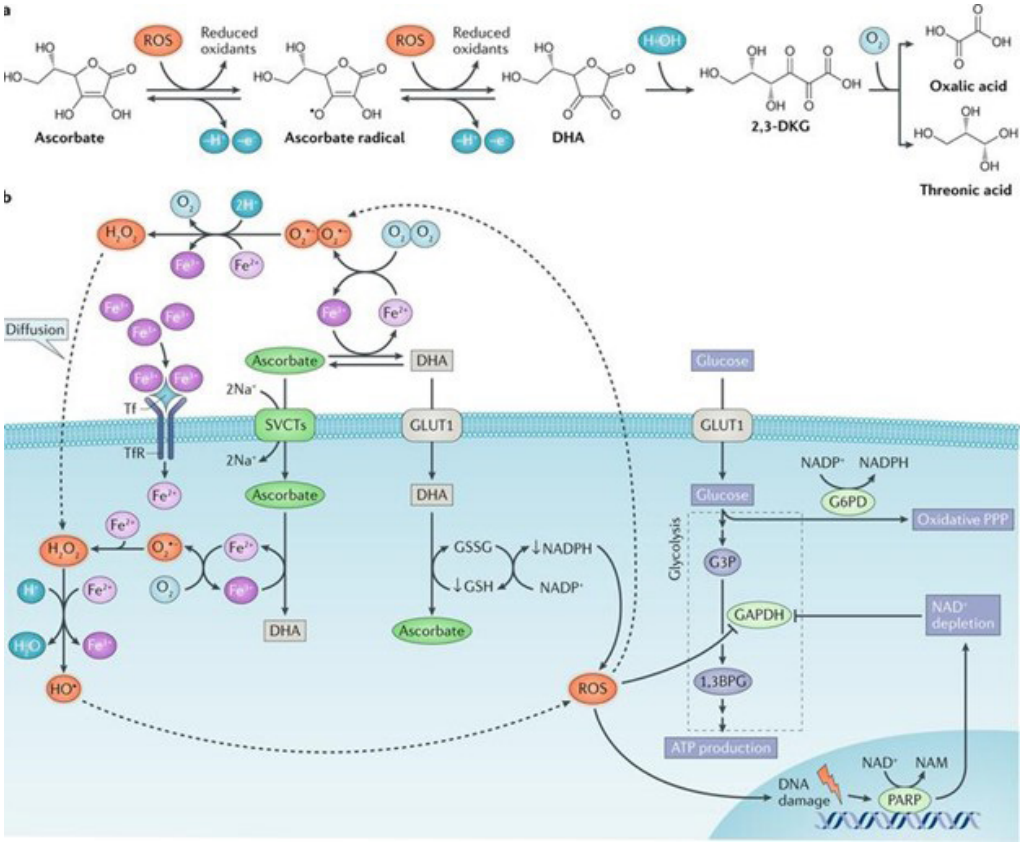
In contrast, because intravenous administration bypasses intestinal absorption, plasma concentrations are elevated to pharmacologic concentrations (mmol/L [mM] values) that cannot be achieved orally.[52] For example, oral administration of 1.25 g of ascorbate achieved a maximum plasma concentration of 134.8 ± 20.6 µmol/L, while IV administration achieved a maximum plasma concentration of 885 ± 201.2 µmol/L.[47,48] Some studies have found that PA is absorbed preferentially by solid cancerous tumors, as compared with normal tissue.[52-55]

There is a substantial body of in vivo and in vitro literature that documents potential anti-tumor effects of ascorbate, demonstrating cytotoxicity toward cancer cells and a slowing of tumor growth.

The biochemistry of ascorbate in relation to cancer is visualized in Figure 2.[56] Several mechanisms have been proposed as underlying the anticancer effects of IV PA. One hypothesized pharmacokinetic pathway involves enzymes of 2-oxoglutarate-dependents (2-OGDDs) that require ascorbate as a cofactor. These enzymes neutralize cancer cells through inducing apoptosis or inhibiting DNA repair. As ascorbate is oxidized to dehydroascorbate (DHA), significant quantities of hydrogen peroxide are produced through autoxidation of supraphysiological concentrations of ascorbate and stimulation of 2-OGDDs. High concentrations that are achievable only with IV PA generate hydrogen peroxide and reactive oxygen species (ROS) via reactions with organometallic species and metal ions, such as iron, that appear to be selectively cytotoxic to cancer cells.

Malignant cells are also typically deficient in enzymes such as catalase, glutathione peroxidase, and peroxiredoxin-2 that reduce peroxide, resulting in prolonged exposure to oxidative stress and an inability to engage in cell repair.[57] This oxidative stress preferentially targets potentially circulating micrometastases of CIS cells. As ascorbate and metabolites are excreted via the bladder, this provides a direct means of promoting the restoration and repair of the epithelium. A recent study indicated that PA also stimulates the formation of T cells and enhances the cytotoxic activity of adoptively transferred CD8 T cells, effectively enhancing the anticarcinogenic properties of the tumor microenvironment.[58] DHA is responsible

**Figure 2.** Integrated Pro-oxidant Mechanism of Vitamin C and Cancer Cell Cytotoxicity[56]




for observations that IV PA functions as an antioxidant agent that reduces free radicals of oxygen, nitrogen, and sulfur, while also enhancing antioxidant impacts of tocopherol (vitamin E).

Effectively, IV PA maintains the integrity of DNA in healthy tissues, amino acid residues, and lipids, reducing oxidation from ROS while targeting malignant tissue. In summary, as a pro-oxidant, high levels of ascorbate that are achievable only with IV PA generate hydrogen peroxide in cancer cells through organometallic reactions that appear to be selectively cytotoxic to cancer cells and prevent their growth and spread. Moreover, as an antioxidant, high levels of DHA protect normal cells in particular against free radicals and are toxic to cancerous cells.[59]

Supporting evidence for these anticancer functions of IV PA derives from work at the National Institutes of Health (NIH), under Mark A. Levine, where PA has been investigated for more than a decade and from extensive experimental studies carried out at Cornell Weill by Cantley and Yun.[45] In discussing possible mechanisms of action, one NIH researcher hypothesized that intravenous levels of ascorbate possibly function as a pro-drug that releases free radicals of unbound oxygen atoms that target malignant cells while having no impact on healthy ones.

In the Levine group's systematic review at NIH, Nauman et al articulated plausible biochemical pathways[60]: "Two mechanisms include increased pro-oxidant damage that is irreparable by tumor cells and oxidation of ascorbate into dehydroascorbic acid (DHA), which is an unstable metabolite and can be cytotoxic. Most data indicate that the first pathway predominates, specifically by generation of extracellular hydrogen peroxide (H2O2) by pharmacologic ascorbate and a trace transition metal, usually iron . These ROS have multiple downstream effects, including but not limited to, DNA damage, mitochondrial damage, and stimulation of apoptotic pathways.

A retrospective chart review of 7 years of experience at Thomas Jefferson University Hospital for the use of IV PA reported few adverse events and general improvements in fatigue and well-being as well as overall symptom control.[61] More recently, several researchers have reported that renal cells with loss of Von Hippel-Lindau (VHL), a tumor suppressor that destabilizes hypoxia-inducible factor (HIF1) via ubiquitination, have increased transcriptional activity in contrast to VHL-proficient cells and are sensitive to IV PA.[45] Where cancers include increased DNA damage, for instance from radiation therapy or through germ line inheritance of certain BRCA genes, PA appears to selectively impair disease.

Another analysis of preclinical and clinical applications of PA identifies several distinct mechanisms that can account for anticancer properties that have been reported to date; these include an increase in NK cells and in antioxidant activities.[62] A concurring evaluation notes that PA clinically modulates both innate and adaptive immune functions and improves the performance of checkpoint inhibitors in early phase clinical trials.[49] Cantley and colleagues have shown that PA targets some mechanisms that cancer cells exploit for

their proliferation. They note that PA "can target three vulnerabilities many cancer cells share: redox imbalance, epigenetic reprogramming and oxygen-sensing regulation."

Overall, mistletoe and IV PA share several mechanisms of action that may be relevant to the anticarcinogenic outcome from their combined use. Clinical investigators have documented numerous studies finding that intravenous ascorbate achieves pharmacological levels that promote tumor suppressor genes in cancer cells and interact favorably with chemotherapy agents.[63] Both mistletoe and IV PA can activate NK cells, enhance growth and maturation of T-cells, enhance DNA repair enzymes, and induce dose-dependent, pro-apoptotic death of tumor cells. It has been suggested that because of the inherent catalase deficiency of tumor cells, malignant cells are especially susceptible to high-dose PA.[40,64]

## Nutraceuticals

In addition to the above uses of mistletoe and IV PA, the patient in the current case study relied on several products shown to have potent anticarcinogenic properties in some experimental and clinical studies, such as Wilken et al,[65] including one commercial product that combines many relevant compounds. Metabolic Synergy, from Designs for Health (Suffield, Connecticut, USA), contains a number of key antioxidants including alpha-lipoic acid, taurine, inositol, and epigallocatechin gallate (EGCG). In addition, other daily supplementation in the current case study included curcumin, vitamin D3; and Chaga, Ganoderma, Reishi, Lions Mane, and Turkey Tail mushrooms.

**Curcumin, 1500 mg.** A number of studies have confirmed that curcumin has the capacity to suppress several types of cancer cells, including soft-tissue sarcoma and melanoma.[66] Curcumin also inhibits both NF-kappa beta protein-1 (AP-1) activation and has synergistic effects combined with the Viscum extract, as well as inhibiting angiogenesis.[67,68]

**Vitamin D3, 5000 mg.** Calciferol with vitamin K2 has been shown to inhibit inflammation and carcinogenesis in a variety of cell lines.[67,69] In addition, epidemiological studies have found that those with the highest cancer risks have the lowest plasma levels of these vitamins.[70,71]

**Mushrooms.** Chaga, Ganoderma, Reishi, Lions Mane, and Turkey Tail are among the parasitic mushrooms that have been found to have medicinal properties relevant to suppression of aberrant cell growth, including inhibitors of mitotic kinase and angiogenesis and promotors of apoptosis.[72]

These anticarcinogenic fungi are also consumed daily at doses of 500 mg per ingestion of Stamets7 from Host Defense, (Olympia, Washington, USA), which contains Lions Mane *(Hericium erinaceus),* Turkey Tail *(Trametes versicolor),* and Chaga (*Inonotus obliquus).* These constitute rich sources of polyphenols, polysaccharides, glucans, terpenoids, steroids, cerebrosides, and proteins. Lions Mane includes metabolites of erinacines derived from the mycelium and hericenones derived from fruiting bodies that have been demonstrated to have antimetastatic activity against several cancer cell lines.

Like the parasitic plant mistletoe, Chaga is an opportunistic fungus that grows on birch trees in cold northern climates and has a long history of use for cancer treatment in Russia, China, Korea, and Japan. These immunomodulatory plants are rich in polysaccharides that have been shown to have potent antimetastatic activities as well.[71]

**Alpha Lipoic Acid (ALA), 200 mg.** ALA improves mitochondrial respiration and protects against DNA damage that leads to the production of cancer cells.[73] It prevents metastases by reducing the activity of enzymes key to carcinogenesis, increases the availability of antioxidants within cells, and reduces cellular damage. This compound also inhibits proliferation and increases apoptosis in some cancer-cell lines, including colon and breast cancers.[72]

**Omega-3 fatty acids (Omega 3), 2000 mg.** These fatty compounds found in fish, chia seeds, and Cruciferae have been shown experimentally to suppress the growth of bladder cancer cells, both in in-vitro and in-vivo studies. Alpha-linolenic acid (ALA) is found mainly in plant oils and seafood and constitutes an excellent source of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids. Omega-3 was found to inhibit the development of premalignant and malignant lesions in a rat model of bladder cancer, possibly due to anti-inflammatory, antioxidant, antiproliferative, and anti-angiogenic properties.[74]

**Melatonin, 20 mg qd nightly.** As a naturally produced hormone, melatonin has a wide range of physiological properties including oncostasis, possibly because it inhibits angiogenesis by repairing damage and suppressing growth factors. High doses are under investigation now at several cancer institutes for possible use not only as an anticancer agent but also as an aid to improve sleep when ingested prior to sleep. For hormonally dependent breast cancer, low serum levels of melatonin have been associated with a poor prognosis, while blind women with naturally higher levels of melatonin have significantly less breast cancer.[75] In combination with other agents, melatonin appears to improve cancer treatment at high doses through various oncostatic impacts.[70]

## Cautions

As with any experimental intravenous treatment, the research team carefully considered the risk of anaphylaxis in the current case study. To avoid that possibility, the intravenous doses were administered at the rate of 5 mL/minute. The biologically effective doses of intravenous mistletoe mali were titrated to the point where within 48 hours of administration, the patient experienced pyrexia; urticaria; and flu-like, inflammatory responses, lasting for periods of 24 to 48 hours, with temperature elevation between 37.5°C and 38°C. During maintenance, subcutaneous mistletoe was provided on alternative days to IV, to elicit localized erythema the size of a quarter and also induce a generalized immunological response as indicated by a temperature of 38°C.

### Cost

Urinary cancer of the bladder has high, lifetime-treatment costs, with estimated expenditures of approximately $187 000 per patient, and in 2010, a total annual cost of approximately $4 billion to treat patients.[76] Analyses of costs of different treatments within the Surveillance, Epidemiology and End Results (SEER)–Medicare database have found no association between survival and either the intensity or frequency of the surveillance protocols.[77,78] Global supply shortages of BCG are likely to remain problematic for some time.

Mistletoe treatment can involve different types of mistletoe, notably mali, abietis, and pini, with the latter two being used chiefly for subcutaneous administration and the former applied both for intravenous and intravesical instillation. Currently mistletoe is FDA approved for use as an ingested liquid treatment for migraines.

Glass vials (2 cc) can be acquired from one of the major commercial producers and cost about $20-$40 each, depending on the strength of the material, for use with 10, 20, 40, and 100 mg of the treatment. Expenses for administration are relatively low, because most patients can learn to deliver their own subcutaneous injections.

Because no special toxic control policies are required, unlike traditional chemotherapy agents, no additional costs occur for disposal systems for hazardous medical waste and protective personal equipment. For patients diagnosed in 2011, median annual costs of trimodal therapy of TURB and of chemo- and radiotherapy, at $827 million, were nearly double those for cystectomy at $492 million, although survival was longer in the latter group.[79]

## SUMMARY

Thoroughly detailed clinical case reports, sometimes conducted on researchers themselves, have had profound impacts on the history of medicine. For instance, a single well-depicted case study catheterizing the human heart laid the foundation for modern interventional cardiology.[80] In 1929, a 25-year-old German physician, Werner Forssman, reported performing the procedure on himself. In 1956, he won the Nobel Prize in medicine for this pioneering work, with physicians Andre Cournand and Dickinson Richards.

In the single case reported in the current study, the patient's early life history of industrial chemical exposures and her lack of smoking or use of hair dye leave little doubt that environmental carcinogens played a major role in producing this unusual cancer for a female with no relevant genetic risk factors.

To the best of the current research team's knowledge, this is the first case where IV PA and mistletoe, plus intravesical and subcutaneous mistletoe, have been employed in the complete remission of high-grade CIS, NMIBC refractory to BCG. The integrative therapeutic approach undertaken was designed to alter the endogenous milieu by employing combined xenobiotic agents to enhance their net anticarcinogenic properties. The combined treatments relied on in the current case study likely led to the more than 78-month remission for the patient who has thereby avoided costly, complex, and complicating surgeries, including cystectomy.

Of course, this case report constitutes an N of one. At the same time, spontaneous resolution wasn't expected given the refractory and progressive nature of the patient's cancer, her advanced age, and the generally poor prognosis for salvage treatment of the high-grade CIS that was NMIBC refractory to BCG.

The treating physicians concur that several factors including the patient's overall good health, ability to tolerate treatments and self-administer the subcutaneous mistletoe, and incorporation of nutraceuticals and stress reducing practices such as yoga and meditation, appear salient to the successful outcome. Instillation directly into the bladder of mistletoe has now been shown to be well-tolerated in Phase I and II studies and is currently undergoing Phase III investigation in a European study for NMIBC as a followup to the report by A. Rose, 2015, led by Jurgen Eisenbrau. Whether BCG/3 with interferon may have also played a role in the current study is a possibility that can't be excluded, although that treatment was only applied at the initiation of treatment following the failure of BCG and wasn't part of maintenance treatments. In addition, the systemic immunological impacts of intravenous PA and intravenous, intravesical, and subcutaneous mistletoe are also under active investigation in ongoing and recently completed clinical trials.

As with the mistletoe trial at Hopkins, the IV PA intervention is undergoing a resurgence of interest, chiefly for salvage therapies for patients who have exhausted conventional oncology treatments, as indicated in the PDQ summary posted on the NCI website. It appears especially promising when combined with chemotherapy.[26] Mechanisms that appear to be relevant include the fact that the pharmacologic doses used in the current case study resulted in supersaturation levels. PA is quickly excreted, with a half-life of about two hours in healthy patients, so that levels are normalized to physiological levels within 16 hours of IV infusion.

In contrast, for cancer patients, the hypoxic tumor environment appears to enhance retention and uptake of PA for up to 48 hours, with this prolonged retention possibly enhancing antioxidant capacities.[46] In addition, like mistletoe, IV PA has been documented both experimentally and clinically to augment the proliferation of NK cells and enhance apoptosis.

At present, integrative oncology and functional-or health medicine centers[81] using some of these therapies have opened at George Washington University Medical Center, the Toronto Center for Functional Medicine, the Ottawa Integrative Cancer Center, Johns Hopkins University, and a growing number of other programs in the USA, Canada, and Europe.[82] In all relevant trials of mistletoe or IV PA reported to date, no major adverse impacts have been noted, and indeed several have indicated positive synergistic effects to enhance efficacy and reduce side effects of both radiotherapy and chemotherapy.

The challenge for integrative oncology to evaluate scientifically combined therapies is considerable. The importance of the current case study is that it represents a successful salvage treatment for a costly refractory disease, which adopted an integrative approach using mistletoe together with IV PA. The combined protocol employs a number of practices currently used in many integrative cancer centers.

As the field of integrative oncology continues to mature, it will be critically important to document additional cases like the current one to drive future research. Such combined treatments may also necessitate a rethinking of the role of RCTs, because substantial methodological challenges exist to studying the use of multiple treatments at the same time. Whether sequential case analyses, case series, or cross-sectional comparisons may offer some value in such circumstances is a matter that merits serious consideration, given the mounting costs of cancer and growing reliance on combined therapies.

Results of the above-described phase III European trial sponsored by Abnova of intravesical mistletoe for NMIBC are expected to be made public within two years, and those of the Phase I Hopkins trial have already clarified that there are few side effects and improvement in QoL, with some indication of lack of disease progression in 25% of the study population. In parallel, developing and validating the combined therapy for an expanded case series of high-grade CIS is a matter of some urgency in light of the major supply disruptions for and considerable costs of BCG, the expense of implementing current protocols and salvage therapies, and complicated prognosis for refractory cases.

## CONCLUSIONS

This study is the first reported instance of combined treatments to achieve complete remission for high-grade NMIBC refractory to BCG and MIT-C, using intravesical, subcutaneous, and intravenous mistletoe and intravenous ascorbate. It includes pharmacological information on possible mechanisms. In light of the global shortage of BCG, the high proportion of cases refractory to BCG and MIT-C, the unproven use of costly off-label pharmaceuticals, such as gemcitabine, and the relative cost-effectiveness of mistletoe and PA, clinicians should give serious consideration to employing these combined functional medicine treatments for BCG- and MIT-C-refractory NMIBC. Further research is needed with additional patients that can advance understanding, including standardization of methods for systematically evaluating combined therapies—blinded and non-blinded, nomenclature regarding mistletoe preparation, doses, concentrations, regimes of administration, lengths of treatment, targeted cancer types, and other aspects.

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## AUTHORS' DISCLOSURE STATEMENT

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