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Original Research Article

Mistletoe extract (Iscador®) in cancer patients undergoing chemotherapy for prostate and bladder tumors: A prospective observational study

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Abstract

Objective: While mistletoe (a semi-parasitic evergreen plant) extract is commonly used as a complementary therapy in Europe, the evidence for its efficacy against the toxicity of chemotherapy is mixed. Our study aimed to evaluate the impact of mistletoe extract as a complementary therapy on the health-related quality of life (HRQoL) and hematological toxicities in patients with metastatic prostate and bladder cancers undergoing chemotherapy.

Materials and Methods: This observational study prospectively involved patients with metastatic prostate and bladder cancers treated with either chemotherapy alone or in combination with Iscador®, a mistletoe extract. The study's primary outcome was HRQoL assessed at baseline and after each chemotherapy cycle. Secondary outcomes included hematological toxicities.

Results: A total of 116 patients, including 59 with prostate cancer and 57 with bladder cancer, were enrolled. Analysis of the HRQoL symptom scales of prostate cancer patients revealed significant improvement in fatigue (p=0.014), pain (p=0.023), insomnia (p=0.017), and diarrhea (p=0.031) in the mistletoe extract group compared to the control group. In bladder cancer patients, no significant differences were observed in the HRQoL scales between the two treatment groups. Moreover, no significant differences were found between the mistletoe extract and control groups regarding hematological toxicities.

Conclusion: Our study showed that mistletoe extract significantly improved four scales of HRQoL in prostate cancer patients undergoing chemotherapy. However, in patients with bladder cancer, the addition of mistletoe extract to chemotherapy does not appear to have a substantial impact on HRQoL, and thus, it should not be considered a complementary therapy for these patients.

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Introduction

Chemotherapy is a widely used treatment modality for prostate and bladder cancers (Amjad, Chidharla et al. 2020). Despite its substantial therapeutic benefits, it is often accompanied by adverse effects such as alopecia, anorexia, cachexia, cephalalgia, fatigue, gastrointestinal disturbances, dermatological reactions, myalgia, and an elevated risk of infections (Jesslyn 2023, Xiao, Zhang et al. 2024). These side effects can significantly diminish the patient's health-related quality of life (HRQoL). Consequently, there is an intensive effort to optimize the treatment to minimize these adverse events while maximizing therapeutic efficacy. Clinical studies indicate that complementary medicine can play a crucial role in this context, enhancing the tolerability of the treatment process and potentially improving patient survival outcomes (Yarnell and Zimmerman 2019).

Plant-derived drugs are frequently employed as complementary therapies to enhance the efficacy and tolerability of primary cancer treatments (Dehelean, Marcovici et al. 2021). Among these, Mistletoe extract (*Viscum album* L) has a long history as a medicinal plant in cancer care (Thronicke, Schad et al. 2022). Mistletoe extract is distributed in many parts of the world and has been widely used as a supportive therapy for different cancers (Majeed, Hakeem et al. 2021). Some of its properties are attributed to lectins, viscotoxins along with phenolic acids, flavonoids, alkaloids, terpenoids, and polysaccharides (Szurpnicka, Kowalczuk et al. 2020, Kleszken, Timar et al. 2022).

Iscador®, a commercially available mistletoe extract, is frequently prescribed as a complementary medicine in cancer treatment, particularly in European countries (Kienle and Kiene 2010, Ostermann, Appelbaum et al. 2020). Systematic reviews reported a medium-sized effect for mistletoe extract on HRQoL, considering the heterogeneity of tumor types (Büssing, Raak et al. 2009, Büssing, Raak et al. 2012, Pelzer, Loef et al. 2022). While some studies have used validated instruments to assess HRQoL in cancer patients receiving Iscador®, many others have focused on indicators of psychosomatic self-regulation and overall quality of life without using these specific tools (Grossarth-Maticek and Ziegler 2008, Marvibaigi, Supriyanto et al. 2014, Loef and Walach 2020, Ostermann, Appelbaum et al. 2020).

Since the efficacy and safety of Iscador® in urogenital cancers remain largely unexplored to date, we aimed to prospectively investigate its impact on patient-reported outcomes and hematological toxicities in patients with prostate and bladder cancers. To our knowledge, this is the first study specifically assessing the adjunctive use of mistletoe extract using different domains of HRQoL and hematological toxicities in patients with metastatic prostate and bladder cancers receiving standard chemotherapy.

Materials and Methods

Study design

This prospective cohort study was conducted at the Shohada-e Tajrish and Atieh Hospitals in Tehran, Iran, between April 2022 and April 2024. Data on HRQoL and hematological toxicities were collected at baseline and after each chemotherapy cycle, for up to 4 to 8 cycles, depending on the cancer type and treatment regimen.

Inclusion criteria were: (1) histologically confirmed metastatic prostate or bladder cancer, (2) eligibility for systemic chemotherapy, (3) performance status 0–2, (4) adequate baseline bone marrow and liver function, and (5) written informed consent.

Exclusion criteria were: (1) previous treatment with mistletoe extract, (2) severe comorbidities contraindicating chemotherapy, (3) uncontrolled infections, and (4) incomplete baseline clinical or

laboratory data. Table 1 shows the patients' baseline characteristics. Our study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, approved the protocol (IR.SBMU.UNRC.REC.1401.005).
Written informed consent was obtained from the patients. To reduce potential biases, inclusion criteria were strictly applied, and data were collected prospectively. While randomization and blinding of treatments were not feasible in this real-world setting, the data were adjusted for baseline characteristics during analysis to minimize confounding.

Table 1. Baseline characteristics of patients

Baseline parameter	Control (n = 67)	Iscador (n = 49)
Tumor type, n (%)		
Prostate	35 (52.2)	24 (49.0)
Bladder	32 (47.8)	25 (51.0)
Sex, n (%)		
Male	64 (95.5)	48 (98.0)
Female	3 (4.5)	1 (2.0)
Age,		
Mean (SE), years	66.24 (1.15)	69.24 (1.12)
Height,		
Mean (SE),cm	171.06 (0.90)	170.58 (1.12)
Weight,		
Mean (SE), kg	72.79 (1.81)	72.81 (1.76)
Serum Creatinine,		
Mean (SE), mg/dl	1.26 (0.04)	1.22 (0.05)
Hemoglobin,		
Mean (SE), g/dl	11.97 (0.27)	12.09 (0.28)
Neutrophils,		
Mean (SE), 10^3cells/µl	4.98 (0.44)	4.80 (0.32)
Lymphocytes,		
Mean (SE), 10^3cells/µl	2.11 (0.11)	2.08 (0.16)
Platelets,		
Mean (SE), 10^3cells/µl	262.30 (13.14)	261.98 (12.44)

Treatment protocol

The control group received chemotherapy alone, while the mistletoe extract group, in addition to chemotherapy, received Iscador® treatment according to the company's recommendation. Group allocation was based on chronological assignment, with the first 49 patients receiving chemotherapy plus mistletoe extract, and the subsequent 67 receiving chemotherapy alone.

The chemotherapy protocol for the treatment of metastatic prostate cancer consisted of 50 mg/m^2 docetaxel intravenously once every 2 weeks for 8 cycles and 5 mg prednisolone twice daily. The patients with metastatic muscle-invasive bladder cancer (MIBC) were given gemcitabine intravenously at a dose of 1000 mg/m^2 on days 1 and 8, every 21 days for up to 4 cycles. Also, they were given carboplatin (AUC = 4, intravenously) on day 1 every 21 days. The carboplatin doses were adjusted for renal function using the Cockcroft-Gault formula as per label. In summary, prostate cancer patients received 8 cycles of chemotherapy biweekly, while bladder cancer patients received 4 cycles every 3 weeks.

Mistletoe extract therapy

The product used was Iscador® Qu, a commercially available herbal fermented aqueous extract of *V. album* L (European mistletoe) grown on Quercus, manufactured by Iscador AG, Switzerland. Iscador® was given subcutaneously in increasing dosage from 0.01 to 20 mg three times per week during the chemotherapy course (Supplementary Table 1). The gradually increasing dosage is intended to prevent type I hypersensitivity reactions. One-level dose reductions were considered for cases of hypersensitivity. Iscador® treatment was started with a bundle pack of Iscador series 0 (Supplementary Figure 1). After every two packs, there is a requirement for a four-day pause in injections. The type of Iscador® is also selected based on the primary tumor (Supplementary Table 2).

Outcomes

The primary endpoint was HRQoL measured by the European Organization for Research and Treatment of Cancer (EORTC) HRQoL questionnaires QLQ-C30 (Aaronson, Ahmedzai et al. 1993) at baseline and after each cycle during the chemotherapy. It is the core scale for

measuring the quality of life of patients with cancer. The questionnaire consists of 30 items, covering five functional scales (physical, role, emotional, cognitive, and social functioning) and nine symptom scales (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The scores are transformed to a 0–100 scale where higher function scores indicate better functioning and lower symptom scores indicate fewer symptoms (Fayers, Aaronson et al. 2001). A translated version of the EORTC QLQ-C30 was validated earlier for use in Iranian cancer patients (Montazeri, Harirchi et al. 1999).

The secondary endpoints were hematological toxicities as assessed at baseline and after each cycle during the chemotherapy using the common terminology criteria for adverse events (CTCAE v.5; Table 2) (Health and Services 2017). Patient-reported outcomes and hematological toxicities were analyzed in all patients with a baseline assessment and at least one post-baseline assessment.

Table 2. CTCAE v.5 grading criteria for hematological toxicities

Toxicity	Grade I	Grade II	Grade III	Grade IV
Anemia	Hgb <LLN - 10.0 g/dl	Hgb <10.0 - 8.0 g/dl	Hgb <8.0 g/dl	Life-threatening consequences; urgent intervention indicated
Neutropenia	<LLN – 1500 mm^3	<1500 – 1000 mm^3	<1000 – 500 mm^3	<500 mm^3
Lymphocytopenia	<LLN – 800 mm^3	<800 – 500 mm^3	<500 – 200 mm^3	<200 mm^3
Thrombocytopenia	<LLN - 75,000 mm^3	<75,000 - 50,000 mm^3	<50,000 - 25,000 mm^3	<25,000 mm^3

Abbreviation: Hgb, hemoglobin; LLN, lower limit of normal

Statistical analysis

The baseline-adjusted scores for all functional and symptom scales of HRQoL were compared between the control and mistletoe extract groups by the Analysis of covariance (ANCOVA) test. Our analysis approach aligns with a modified intention-to-treat (mITT) principle, analyzing all patients with at least one post-baseline HRQoL assessment. To compare the percentage of ≥ Grade II hematological toxicities between the two groups, we employed Pearson's chi-square test. When cell frequencies were below expected levels, Fisher's exact test was applied to adjust the chi-square probability values. Results were considered statistically significant if the p-value was less than 0.05 (two-tailed). All statistical analyses were conducted using SPSS version 27 (Chicago, Illinois, USA).

The sample size in this observational study was based on the number of eligible patients available during the study period and the accessibility of the investigated drug. Although no formal a priori calculation was performed, this reflects the real-world constraints of conducting observational research and should be taken into account when interpreting the findings.

Results

Patients' characteristics

Of 128 screened patients, 116 patients with prostate (n=59) and bladder (n=57) cancer were eligible and enrolled; Of these, 108 completed baseline and at least one post-baseline assessment and were included in the HRQoL analysis. Thus, eight patients were excluded due to incomplete data. At baseline evaluation, the two groups were relatively homogenous regarding demographic data (Table 1). Although metastatic sites varied, all enrolled patients had a performance status of 0–2, and baseline HRQoL was adjusted statistically to reduce bias. Stratified analysis by cancer type (prostate vs. bladder) helped account for symptom variability from metastatic burden.

HRQoL

As shown in Table 3, among the 9 symptom scales in prostate cancer patients, fatigue (p = 0.014), pain (p = 0.023), insomnia (p = 0.017), and diarrhea (p = 0.031) were significantly improved in the mistletoe extract group compared to the control group. However, there was no significant difference between the groups regarding functional scores of prostate cancer patients after adjustment for the pre-treatment scores (Table 3). In patients with bladder cancer, neither symptom nor functional scales of HRQoL were improved in the mistletoe extract group compared to the control group (Table 4).

Table 3. Health-related quality of life scores in control and Iscador groups of prostate cancer patients

Scales	Baseline-adjusted scores during treatment Mean (SE)		Between-group difference Mean (95%CI)	p value
	Control (n = 29)	Iscador (n = 23)		
Symptom scales*				
Fatigue (FA)	50.3 (4.3)	33.1 (4.9)	-17.2 (-30.6, -3.7)	0.014¶
Nausea and vomiting (NV)	13.3 (3.0)	11.9 (3.4)	-1.4 (-10.5, 7.6)	0.751
Pain (PA)	35.4 (3.5)	22.9 (4.0)	-12.5 (-23.3, -1.8)	0.023¶
Dyspnea (DY)	15.5 (3.1)	12.5 (3.5)	-3.0 (-12.4, 6.4)	0.522
Insomnia (SL)	39.4 (4.4)	22.7 (5.0)	-16.7 (-30.3, -3.1)	0.017¶
Appetite loss (AP)	34.9 (5.2)	23.9 (6.0)	-11.0 (-27.4, 5.3)	0.181
Constipation (CO)	13.3 (3.6)	22.5 (4.1)	9.2 (-2.1, 20.5)	0.109
Diarrhea (DI)	19.0 (3.0)	9.0 (3.4)	-10.0 (-19.0, -0.9)	0.031¶
Financial difficulties (FI)	52.3 (4.5)	46.5 (5.2)	-5.8 (-19.6, 8.0)	0.407
Functional scales#				
Physical functioning (PF)	65.0 (3.2)	69.5 (3.7)	4.5 (-5.5, 14.4)	0.370
Role functioning (RF)	67.1 (4.3)	76.7 (4.9)	9.6 (-3.7, 22.9)	0.153
Emotional functioning (EF)	70.5 (3.0)	70.8 (3.5)	0.3 (-9.0, 9.6)	0.949
Cognitive functioning (CF)	76.4 (3.5)	82.4 (4.0)	6.0 (-4.7, 16.5)	0.267
Social functioning (SF)	71.6 (3.5)	69.9 (4.0)	-1.7 (-12.5, 9.1)	0.749
Global health status (QoL)	55.5 (3.6)	59.3 (4.1)	3.8 (-7.1, 14.7)	0.486

*For symptom scales, higher scores reflect greater symptom severity.
For functional scales, lower scores indicate worse functioning or distress.
¶ All statistically significant *P* values corresponded to small effect sizes: FA, 0.12; PA, 0.10; SL, 0.11; DI, 0.09.

Table 4. Health-related quality of life scores in control and Iscador groups of bladder cancer patients

Scales	Baseline-adjusted scores during treatment Mean (SE)		Between-group difference Mean (95%CI)	p value
	Control (n = 30)	Iscador (n = 26)		
Symptom scales*				
Fatigue (FA)	31.4 (2.7)	35.2 (2.9)	3.8 (-4.1, 11.8)	0.336
Nausea and vomiting (NV)	9.0 (2.4)	10.8 (2.6)	1.8 (-5.3, 9.0)	0.606
Pain (PA)	19.2 (2.9)	24.5 (3.1)	5.3 (-3.2, 13.8)	0.217
Dyspnea (DY)	13.8 (3.5)	17.7 (3.8)	3.9 (-6.5, 14.2)	0.459
Insomnia (SL)	19.5 (3.7)	27.5 (4.0)	8.0 (-3.1, 19.0)	0.153
Appetite loss (AP)	18.7 (3.3)	24.2 (3.5)	5.5 (-4.1, 15.1)	0.260
Constipation (CO)	25.4 (3.6)	23.8 (3.8)	-1.6 (-12.1, 8.9)	0.759
Diarrhea (DI)	3.5 (1.8)	6.6 (2.0)	3.1 (-2.6, 8.7)	0.282
Financial difficulties (FI)	38.1 (4.7)	38.3 (5.1)	0.2 (-13.7, 14.1)	0.978
Functional scales#				
Physical functioning (PF)	73.1 (2.1)	75.5 (2.3)	2.4 (-4.0, 8.7)	0.457
Role functioning (RF)	78.2 (3.0)	79.9 (3.2)	1.7 (-7.1, 10.5)	0.703
Emotional functioning (EF)	76.7 (2.8)	76.2 (3.0)	-0.5 (-8.8, 7.7)	0.897
Cognitive functioning (CF)	87.9 (2.1)	89.1 (2.2)	1.2 (-5.0, 7.3)	0.699
Social functioning (SF)	78.2 (3.3)	73.3 (3.5)	-4.9 (-14.6, 4.7)	0.312
Global health status (QoL)	60.1 (2.7)	63.5 (2.9)	3.4 (-4.7, 11.5)	0.401

*For symptom scales, higher scores reflect greater symptom severity.
For functional scales, lower scores indicate worse functioning or distress.

Hematological toxicities

Our results indicated that hematological toxicities were generally higher in patients with bladder cancer than in those with prostate cancer. A plot of ≥ Grade II hematological toxicities for the mistletoe extract and control groups in prostate cancer patients is shown in Figure 1. Chi-square analysis revealed no significant differences in ≥ Grade II anemia (p =

0.297), neutropenia (p = 0.849), lymphocytopenia (P = 0.427), and thrombocytopenia (p = 0.999) between the mistletoe extract and control groups. Also, a plot of ≥ Grade II hematological toxicities in patients with bladder cancer is shown in Figure 2. Similar to prostate cancer patients, the addition of mistletoe extract to the chemotherapy did not affect the hematological toxicities in bladder cancer patients (anemia, p = 0.662; neutropenia, p = 0.459; lymphocytopenia, p = 0.850; and thrombocytopenia, p = 0.576).

Mistletoe side effect

The compliance and tolerability of mistletoe extract administration were acceptable, with mild toxicity. However, eight patients (three with prostate cancer and five with bladder cancer) experienced a local skin reaction to the injection. Local reactions at the injection site did not lead to treatment interruption. However, two patients with prostate cancer and two with bladder cancer reported large local skin reactions, which resulted in one-level dose reductions.

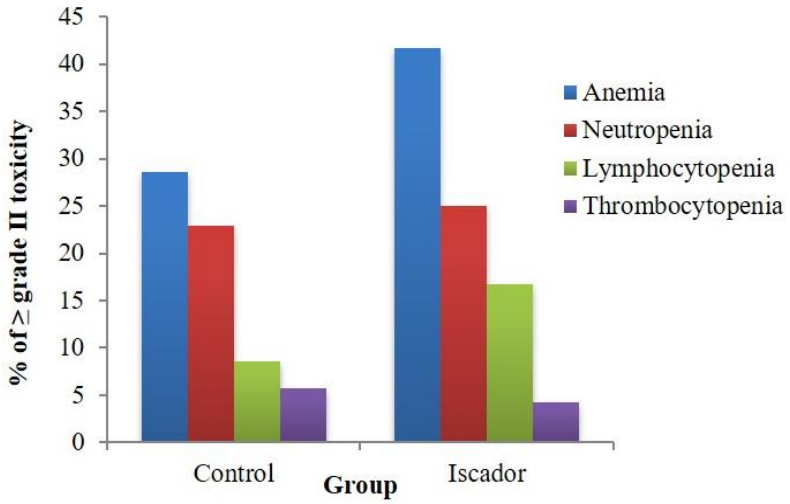

Figure 1. Bar chart showing the percentage of ≥ Grade II hematological toxicities in the mistletoe extract and control groups of prostate cancer patients.

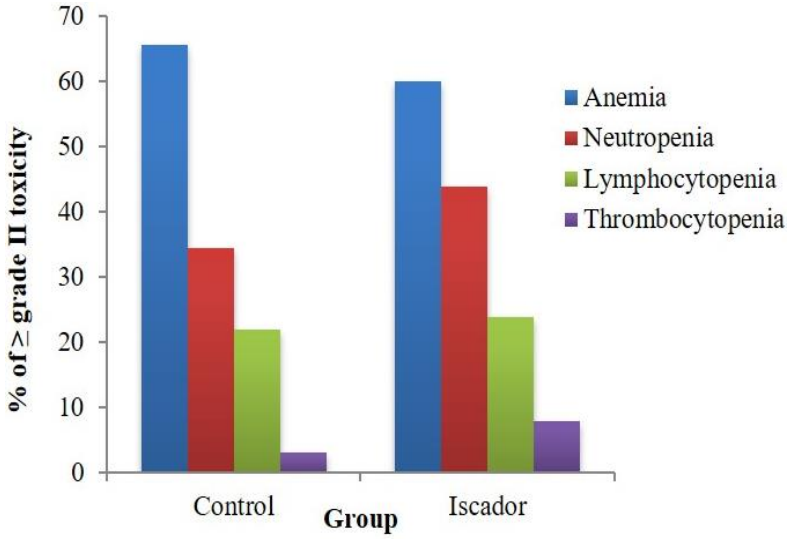

Figure 2. Bar chart showing the percentage of ≥ Grade II hematological toxicities in the mistletoe extract and control groups of bladder cancer patients.

Discussion

Chemotherapy significantly affects HRQoL in patients with advanced urogenital cancers. Despite widespread use of mistletoe extract in Europe, evidence regarding its role in prostate and bladder cancers remains inconclusive. Our findings bridge this gap by providing prospective, real-world data on HRQoL and toxicity outcomes, particularly highlighting Iscador benefits in prostate cancer. These insights may inform future integrative oncology practices, especially for symptom management during chemotherapy.

The use of mistletoe extract in cancer treatment has been examined in some systematic reviews, and its effectiveness as a complementary therapy remains a topic of debate. Some authors indicated that mistletoe treatment offers a clear benefit regarding quality of life (Melzer, Iten et al. 2009, Kienle and Kiene 2010), while others showed that it has no benefit for cancer patients (Ernst, Schmidt et al. 2003). We concluded that the mistletoe extract efficacy may be linked to the cancer types and chemotherapy regimens.

To the best of our knowledge, this is the first study assessing the impact of mistletoe extract as a complement to chemotherapy on HRQoL and hematological toxicities in patients with prostate and bladder cancers. Our findings showed that the administration of Iscador® could result in significant improvements in key HRQoL symptom scales, including fatigue, pain, insomnia, and diarrhea in prostate cancer patients undergoing chemotherapy with docetaxel. Quality of life is affected in various aspects of prostate cancer. Pain and fatigue symptoms, along with physical and emotional functions, are the most prominent parameters that are aggravated in patients with metastatic prostate cancer undergoing chemotherapy (Charalambous and Kouta 2016, Popiołek, Brzoszczyk et al. 2022). Although Iscador® did not significantly enhance functional aspects of HRQoL, such as physical and role functioning, it notably alleviated common chemotherapy-related symptoms. These results align with several studies that have demonstrated mistletoe extract positive impact on fatigue, pain, diarrhea, and insomnia in other cancer types including breast, lung, pancreatic, gastric, and osteosarcoma cancers (Eisenbraun, Scheer et al. 2011, Kim, Yook et al. 2012, Freuding, Keinki et al. 2019, Oei, Thronicke et al. 2019, Loef and Walach 2020, Oei, Thronicke et al. 2020, Pelzer, Loef et al. 2022, Staupe, Buentzel et al. 2023, Wode, Kienle et al. 2024). Oei et al. (Oei, Thronicke et al. 2020) showed that mistletoe extract co-administration in breast cancer could enhance the overall efficacy of chemotherapy by reducing fatigue and insomnia. Also, the application of mistletoe extract significantly improved diarrhea in patients with breast and gastric cancers (Eisenbraun, Scheer et al. 2011, Kim, Yook et al. 2012). According to Kim et al. (Kim, Yook et al. 2012), the beneficial effect of mistletoe therapy on diarrhea may be attributed to its immunomodulatory properties, which could potentially prevent apoptosis in the normal gut mucosa.

Giesinger et al. (Giesinger, Kuijpers et al. 2016) estimated thresholds for the clinical importance of key QLQ-C30 scales including fatigue and pain. They showed that a score of 39 points or higher indicates clinically significant fatigue. Also, a threshold of 25 points or higher represents clinically important pain levels. As indicated in Table 3, our results in prostate cancer patients showed that mistletoe extract alleviated the fatigue score from 50.3 to 33.1 and improved the pain score from 35.4 to 22.9, representing the clinical efficacy of mistletoe extract in this setting.

Unlike patients with prostate cancer, the administration of Iscador® in bladder cancer patients did not improve HRQoL scales. A recent study in pancreatic cancer patients also failed to detect any significant difference in HRQoL between the mistletoe extract and control groups. The number and severity of general adverse events were also similar (Wode, Kienle et al. 2024). Also,

Bar-Sela et al. (Bar-Sela, Wollner et al. 2013) demonstrated that mistletoe did not affect the quality of life in lung cancer patients treated with carboplatin.

While chemotherapy generally reduces the quality of life in cancer patients, the type of treatment is also crucial. Docetaxel, as a chemotherapy agent for advanced prostate cancer, is reported to be the main cause of fatigue and physical function decline (Bergin, Hovey et al. 2017, Lehtonen 2023). The observed benefits of Iscador® in prostate cancer may suggest a clinical role for mistletoe extract in improving the tolerability of docetaxel therapy, potentially through its anti-inflammatory and immune-modulatory properties (Oei, Thronicke et al. 2019). Previous studies have shown that mistletoe extract stimulates both innate immunity and the adaptive immune response (2015, Beztsinna, de Matos et al. 2018)**.** The lack of benefit in bladder cancer patients in our study may be attributed to the distinct biological characteristics of bladder tumor cells or the chemotherapy regimen used (Juengel, Rutz et al. 2023). A recent preclinical study on different breast cancer cell lines with varying metastatic potentials might explain these results. Iliev et al. (Iliev, Tsoneva et al. 2024) showed that the combination of Iscador® and docetaxel is more potent than Iscador® and cisplatin in highly metastatic breast cancer cell lines. In cell lines with low metastatic potential, increasing the dose of Iscador® with cisplatin reduced the IC_{50} more effectively than with docetaxel. An *in vitro* study on cisplatin-resistant lung cancer cells demonstrated that mistletoe extract itself exhibits greater antiproliferative effects compared to cisplatin (Kim, Kim et al. 2017).

An important finding of this study was the lack of significant differences in hematological toxicities between the control and mistletoe extract groups. This result aligns with previous studies, which have not reported severe adverse effects of mistletoe (Oei, Thronicke et al. 2019). A systematic review of several cancers, including breast, colorectal, gastric, ovarian, and lung cancers, demonstrated that mistletoe has no significant toxic effects on patients undergoing chemotherapy and, in some cases, has ameliorated the side effects of treatment (Freuding, Keinki et al. 2019). Notably, a study by Bar-Sela et al. (Bar-Sela, Wollner et al. 2013) demonstrated that Iscador®, when combined with carboplatin for lung cancer treatment, did not increase hematological toxicities or other severe side effects, further supporting its safety profile in oncology settings. Therefore, the lack of significant toxicity in our study groups suggests that Iscador® could serve as a valuable adjunct to chemotherapy for prostate cancer, enhancing patient quality of life without exacerbating chemotherapy-related side effects.

The lack of blinding and randomization is considered the main limitation of our study. Expectations are believed to drive the 'placebo effect', which influences both perceptions and biological processes (Oeltjenbruns and Schäfer 2008). Invasive treatments like injections tend to elicit a stronger placebo response compared to oral medications (Diener, Schorn et al. 2008). It is important to recognize that the placebo effect is a genuine, measurable aspect of an organism psycho-neurobiological response, and it plays a role in the healing process (Oeltjenbruns and Schäfer 2008). However, Freuding et al. (Freuding, Keinki et al. 2019) noted that using a placebo injection in the control group is impractical because subcutaneous injections of mistletoe preparations can cause local reactions, which would inadvertently reveal the treatment to both patients and healthcare providers. Another limitation is the relatively small sample size. Our study was not powered to detect interactions by age, performance status, or baseline HRQoL. Future studies with larger cohorts should explore these subgroups. Also, larger randomized trials are necessary to elucidate the specific mechanisms and contexts that

determine the efficacy of Iscador® across different types of cancer. Kristensen et al. (Kristensen, Solheim et al. 2017) suggested that the timing of HRQoL assessments can influence the likelihood of detecting differences in HRQoL. Thus, assessing outcomes midway through chemotherapy cycles may lead to better discrimination in HRQoL scales. However, the use of a comprehensive 30-item quality of life questionnaire, which assesses a wide range of symptoms, and the implementation of control and treatment groups for both bladder and prostate cancers, may be considered a strength of our study.

In conclusion, we found that mistletoe extract can significantly improve key HRQoL symptom scales, including fatigue, pain, insomnia, and diarrhea in prostate cancer patients undergoing chemotherapy. In contrast, for bladder cancer patients, our results suggested that mistletoe extract is unlikely to influence HRQoL scales when used in combination with chemotherapy; therefore, it should not be considered a complementary treatment for these patients. Moreover, we found no significant differences in hematological toxicities between the mistletoe extract and the control groups. The lack of randomization and blinding remains a significant limitation and warrants caution in interpretation. Future randomized trials are necessary to confirm these findings.

Conflicts of interest

The authors declare that they have no competing interests.

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Ethical Considerations

Our study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patients.

Code of Ethics

IR.SBMU.UNRC.REC.1401.005

Authors' Contributions

Conception and design: AJ, AB, AR, BM; acquisition of data: RA, MS, AJ, AR, BM; analysis and interpretation of data: SH, AR, BM; writing, review, and/or revision of the manuscript: SH, RA, MS, AJ, AB, AR, BM. All authors read and approved the final manuscript.

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Supplementary

Treatment protocol

The control group received chemotherapy alone, while the mistletoe extract group, in addition to chemotherapy, received Iscador® treatment according to the company's recommendation. The chemotherapy protocol for the treatment of metastatic prostate cancer consisted of 50 mg/m^2 docetaxel intravenously once every 2 weeks for 8 cycles, and also 5 mg prednisolone twice daily. The patients with metastatic MIBC were given gemcitabine intravenously at a dose of 1000 mg/m2 on days 1 and 8, every 21 days for up to 4 cycles. Also, they were given carboplatin (AUC = 4, intravenously) on day 1 every 21 days. The carboplatin doses were adjusted for renal function using the Cockcroft-Gault formula as per label.

Mistletoe extract therapy

Iscador® treatment was started with a bundle pack of Iscador series 0 (2 x 7 ampoules). The gradually increasing dosage is intended to prevent type I hypersensitivity reactions. Iscador was injected subcutaneously three times a week with increasing strength according to the composition of the series. For each patient, 0.01 to 20 mg per injection has been used, as seen in Supplementary Table 1.

After every two packs, there is a requirement for a four-day pause in injections. The type of Iscador is also selected based on the primary tumor (Supplementary Table 2).

Supplementary Table 1. Iscador series and the time of injection period

Month	Strength	0.01 mg	0.1 mg	1 mg	10 mg	20 mg
1	Series 0	2 amp	2 amp	3 amp		
2	Series I		2 amp	2 amp	3 amp	
3-4	Series II			2 amp	2 amp	3 amp

Supplementary Table 2. The choice of Iscador preparation based on the primary tumor

Localizations of the primary tumor	Recommendation	Alternative
Bladder	Qu	M
Prostate	Qu	P

Iscador® series pack

One serial pack contains 7 ampoules in increasing dose strength. The numbers inside the box indicate the order in which the ampoules have to be injected (Supplementary Figure 1). The series packs are available on the market in a so-called bundle pack (2 packs of 7 ampoules).

Supplementary Figure 1. A bundle pack of Iscador