INTRAVESICAL MISTLETOE EXTRACT FOR ADJUVANT TREATMENT OF SUPERFICIAL URINARY BLADDER CANCER

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Summary

Patients with superficial bladder cancer are mostly treated by transurethral tumor resection and adjuvant intravesical Bacillus Calmette-Guerin (BCG), which was shown to reduce tumor recurrence significantly. However, serious side effects of this treatment promoted the search for other immunoactive substances, which to date have failed to show the equal efficacy as BCG. Therefore, the aim of the present study was to evaluate the effect of intravesically applied aqueous mistletoe extract (ME) with respect to tolerability and recurrence rate. In a phase I/II clinical trial the aqueous ME, standardised to mistletoe lectin, was administered intravesically to 24 patients with urinary bladder cancer of the stages pTa G2 (n=14) and pT1 G2 (n=10). Four to seven weeks after transurethral resection each patient received 6 instillations at weekly intervals with 50 ml of ME at lectin concentrations between 10 ng/ml and 5,000 ng/ml. Clinical follow-up consisted of cytology, cystectomy and random biopsies. The local historical control group consisted of 18 patients with pTa G2 (n=5) and pT1 G2 (n=13) tumors that were treated with 6 BCG instillations after transurethral resection. The tolerability of the ME was very good at all applied concentrations. None of the patients had local or systemic side effects. Within the observation time of 12 months, the patients treated with ME showed a recurrence rate of 8/24 (33 %). In the BCG treated group the recurrence rate was 5/18 (28 %) and therefore similar in both groups. Comparison of blood and urine cytokine levels brought about no significant alterations before and after instillation of ME. Intravesically applied standardized ME could be a potential alternative adjuvant therapy for superficial bladder cancer.

Key words: mistletoe extract, mistletoe lectin, superficial bladder cancer, intravesical treatment

Introduction

Adjuvant intravesical use of Bacillus Calmette-Guerin (BCG) after surgical resection of superficial bladder cancer has been shown to decrease tumor recurrence from about 70 % to 30 % in several studies and therefore has become an established therapy for this tumor entity (1,2). But its benefits are outweighed by its sometimes severe side effects of cystic disorders, fever and single cases of military tuberculosis, as well as death (3,4). These side effects promoted the use of therapies with other immunomodulatory substances, which, however, to date have all failed to show efficacy equal to that of BCG therapy.

Aqueous extracts of the European mistletoe (*Viscum album L.*) have been widely used as an alternative therapy in the treatment of patients with malignant disease for more than 70 years (5, 6). However, there is an obvious discrepancy between the popularity of mistletoe extracts and their classification as a nonconventional treatment modality with unproven efficacy in oncology. Reliable evaluation of the effects of extract preparations is seriously hampered by the fact that the extract composition is complex and markedly depends on the different methods of preparation, the time of harvest and the type of host tree.

In search of the biologically active constituents of the extracts, mistletoe lectins are regarded as most important and were documented to exert a remarkable immunomodulating capacity *in vitro* and *in vivo*, e.g. enhancing the cytotoxicity of natural killer cells against model targets (7), and stimulating the secretion of cytokines such as interleukin-1 (IL-1), IL-6, interferon-γ (IFN-γ), tumor necrosis factor (TNF), and colony stimulating factors (8, 9). Additionally, mistletoe lectins have been shown to possess cytotoxic and apoptosis-inducing properties against a large number of human tumor cell lines *in vitro* (10). Also, *in vivo* an antitumoral effect could be shown (11).

According to these findings, a direct application of mistletoe extract to the tumor surroundings in the bladder is expected to be superior to systemic application. Therefore, the present clinical study was designed to evaluate the tolerability and antitumoral effects of a standardized mistletoe extract in patients with superficial bladder cancer.

Methods

A total of 24 patients with superficial bladder cancer and histopathologically verified pTa G2 (n=14) or pT1 G2 (n=10) lesions, which were treated with complete transurethral resection, were entered into this prospective phase I/II trial according to the inclusion/exclusion criteria. Before admission to the study, patients were physically examined to determine their clinical WHO performance score.

Possible local and systemic adverse events due to the application of the mistletoe extract were described to the patients and all included patients provided informed consent. The majority of the patients were male (n=18) and the age was between 35 and 80 years (median 70 years).

For intravesical treatment an aqueous mistletoe extract (Madaus AG, Köln, Germany) was used, which was standardized to the content of mistletoe lectin by a binding assay as described by Vang et al (12). Therapy was started between 2 and 7 weeks after transurethral resection. Each patient received 6 instillations at weekly intervals with 50 ml of the extract with mistletoe lectin concentrations between 10 ng/ml and 5,000 ng/ml. Two or three patients per group received a dose which was then doubled in the next group. After instillation into the bladder, the extract was retained for two hours.

Recurrences were confirmed by cytology, ureterocystoscopy and histopathological assessment, which were repeated at follow-up 3, 6, 9 and 12 months after the beginning of the instillation therapy. The local historical control group consisted of 18 patients with bladder carcinomas of the stages p Ta G2 (n=5) and pT1 G2 (n=13), who had undergone transurethral resection and were then treated with 6 instillations of adjuvant BCG at weekly intervals.

Results

Of the 24 patients incluced in the study, 14 had pTa G2 tumors and 10 had pT1 G2 tumors. These patients were distributed among the 10 therapy groups as shown in Table 1.

The tolerability of the intravesically administered mistletoe extract was very good at all applied concentrations. In the 30 patients no local or systemic side effects according to WHO grade 1 - 4 have been noted.

After a follow-up of 12 months, 3 of the 14 patients with Ta G2 tumors and 5 of the 10 patients with T1 G2 tumors developed recurrences while 16 patients remained without evidence of disease. This corresponds to an overall recurrence rate of 8/24 = 33 %. The highest rate of tumor recurrence was found in the groups treated with the relative low lectin concentrations of 80 ng/ml and 160 ng/ml, however, no clear correlation between dosage and recurrence could be shown.

The recurrence rate in the mistletoe group was comparable to the BCG treated historical control group, in which 2 of 5 patients with Ta G2 tumors and 3 of 13 patients with T1 G2 tumors developed recurrences. This corresponds to an overall recurrence rate of 5/18 = 28 % (Table 2).

TABLE 1 – Patient data and therapy groups

Group	Patient No.	Sex	Age	Tumor stage	Mistletoe lectin Dose (ng/ml)	Recurrence	Toxicity WHO grade 1-4
1	1	m	77	Ta G2	10	No	No
	2	m	67	Ta G2	10	No	No
2	5	m	71	Ta G2	20	No	No
	6	m	41	Ta G2	20	Yes	No
3	7	m	74	Ta G2	40	No	No
	8	m	76	Ta G2	40	No	No
4	10	m	74	Ta G2	80	No	No
	12	m	71	T1 G2	80	Yes	No
5	13	m	65	T1 G2	160	Yes	No
	14	m	78	T1 G2	160	Yes	No
	15	f	35	Ta G2	160	Yes	No
6	17	m	71	T1 G2	320	No	No
	18	m	66	T1 G2	320	Yes	No
7	19	f	70	T1 G2	640	No	No
	20	m	72	T1 G2	640	No	No
8	22	f	77	T1 G2	1.280	Yes	No
	23	m	61	Ta G2	1.280	No	No
	24	m	74	Ta G2	1.280	No	No
9	25	f	72	T1 G2	2.500	No	No
	26	m	71	Ta G2	2.500	No	No
	27	f	39	Ta G2	2.500	No	No
10	28	m	48	Ta G2	5.000	Yes	No
	29	m	56	Ta G2	5.000	No	No
	30	f	60	T1 G2	5.000	No	No

TABLE 2 – Comparison of recurrence after adjuvant intravesical mistletoe extract and adjuvant intravesical BCG therapy

Stage/Grade	Recurrences after adjuvant mistletoe extract	Recurrences after adjuvant BCG
Ta G2	3/14	2/5
T1 G2	5/10	3/13
Ta G2 + T1 G2	8/24 = 33 %	5/18 = 28 %

Discussion

The primary purpose of adjuvant therapy after transurethral resection of superficial bladder cancer is to prevent a possible recurrence. Intravesical chemotherapy and even more the use of BCG have been shown to be effective in reducing the recurrence rate in patients with pTa and pT1 tumors. Numerous studies were conducted in this group of tumors in the last 20 years and an overall reduction of the recurrence rate from about 70 % (transurethral resection alone) to about 30 % (transurethral resection and adjuvant BCG therapy) could be constated. Therefore, adjuvant intravesical use of BCG has become an established therapy for this tumor entity. Yet, its benefits are outweighed by its sometimes severe local and systemic side effects, which necessitated the search for alternative therapy modalities.

In our study, for the first time standardized mistletoe extract has been used intravesically for adjuvant treatment of superficial bladder cancer. In contrast to BCG, this treatment has been excellently tolerated and none of the patients had local or systemic side effects even at the highest dose of 5,000 ng/ml.

The recurrence rate of the patients included in our study was 33 %. According to a phase I/II study, successively increasing concentrations of the mistletoe extract were used. However, no correlation between dosage and recurrence was found. Additionally, no correlation was observed between tumor stage, grading, and recurrence rate.

The results of this study are in agreement with two preceding animal model studies, which also showed not only a very good tolerability but also antitumoral effects of intravesically applied mistletoe extract or pure mistletoe lectin of doses up to 1,500 ng/ml (13).
To date, there are no controlled clinical data available on the influence of intravesically applied mistletoe extracts on the recurrence rate of superficial bladder cancer.

In our study, the low recurrence incidence after adjuvant mistletoe extract treatment is encouraging and is not the result of patient selection, since the study patients and the local historical controls are comparable with respect to staging and grading. Further studies may help to find the optimal dose and confirm the role of standardized mistletoe in patients with superficial bladder cancer.

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