Reducing Malignant Ascites Accumulation by Repeated Intraperitoneal Administrations of a *Viscum album* Extract

GIL BAR-SELA[1], HADASSAH GOLDBERG[1], DAN BECK[2], AMNON AMIT[2] and ABRAHAM KUTEN[1]

Departments of [1]Oncology and [2]Gynecology, Rambam Medical Center and Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Abstract. *Background: Malignant ascites is a major problem in the management of advanced stages of certain malignancies. The possibility of reducing the accumulation of ascites by intraperitoneal injections of a Viscum album extract (Iscador M®) was evaluated. Patients and Methods: Twenty-three patients, with end-stage malignancies of varying histology, requiring repeated peritoneal punctures, were eligible for analysis. The time-interval between the first two punctures was measured and defined as the baseline. Following each subsequent puncture, Iscador M® 10 mg was injected intraperitoneally. The intervals between later punctures were compared to previous intervals. Results: Following the first injection, the median time-interval between injections increased from 7 to 12 days, reaching 13 days after the second injection. No toxicity was observed. Conclusion: This phase II study suggests that installation of Iscador M® into the peritoneal cavity may reduce the need for repeated punctures. A randomized trial is needed to confirm these promising preliminary results.*

Malignant ascites are a major problem in the management of advanced stages of certain malignancies, including ovarian, pancreatic, gastric and colorectal carcinomas. It is usually a late manifestation of the disease with a mean survival of one to four months following initiation of paracentesis (1). Malignant ascites are frequently associated with substantial symptoms, including abdominal distention and pain, anorexia, restricted mobility, indigestion and dyspnea. Symptom relief is essential for maintaining the quality of life in these patients. Currently, there are no established guidelines for treating malignant ascites (2) and therapy is based mainly on repeated paracentesis. Fluid drainage allows temporary relief, but fluid usually re-accumulates within a few days. Moreover, repeated drainage also causes the reduction of serum albumin levels which, after a certain point, may by itself augment the accumulation of fluid in the peritoneal cavity.

A retrospective Canadian study (3) reported a complication rate of 24%, including bowel perforation, bacterial peritonitis, peritoneo-cutaneous fistula and cellulites, in patients requiring repeated paracentesis. Although this complication rate may vary in different centers, the re-accumulation of fluid and the need for repeated paracentesis have a major impact on patient morbidity. Thus, reducing the need for repeated paracentesis, by preventing fluid accumulation, may improve the quality of life and prevent complications.

The purified *Viscum album* extract (Iscador M®, Weleda AG, Arlesheim, Switzerland) is commonly used by cancer patients as a complementary or alternative medicine (CAM) in several European countries (4). According to some reports, it induces non-specific stimulation of the immune system (5-8). In several reports concerning patients with malignant pleural effusion, pleurodesis was induced by the administration of Iscador M® into the pleural cavity (9, 10). Some investigators claim that the cessation of fluid accumulation is achieved by the stimulation of an antitumour immune reaction rather then by mechanical sclerosis (11). No published study has examined the effect of Iscador M® installation into the peritoneal cavity in patients with malignant ascites.

A prospective pilot study was conducted in patients with malignant ascites requiring repeated paracentesis, in an attempt to evaluate the efficacy and toxicity of repeated Iscador M® administration into the peritoneal cavity. The end-point of the study was to evaluate the rate of fluid accumulation measured by the time-interval between the paracentesis sessions.

Patients and Methods

The eligibility criteria for inclusion in the study were malignant ascites of any origin requiring repeated peritoneal punctures for symptom relief, no active antineoplastic treatment planned and the previous chemotherapy course administered at least four weeks

Correspondence to: Dr. G. Bar-Sela, Department of Oncology, Rambam Medical Center, POB 9602, Haifa 31096 Israel. Tel: 972 4 854-3012, Fax: 972 4 854-2929, e-mail: g_barsela@rambam.health.gov.il

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Table I. *Symptom score.*

Score	1	2	3	4	5
Abdominal pain	No	Seldom	Infrequent	Most of the day	Continuous and severe
Abdominal pressure	No	Slight	Moderate	Severe	Intolerable
Shortness of breath at night	No	Seldom	At least one episode nightly	3-5 episodes every night	Can't sleep due to breathing difficulties
Need for head elevation when supine	1 pillow	2 pillows	3 pillows	Elevated bed	Sleeping in sitting position
Feeling hungry for air	No	Light	Only on effort	After simple daily activities	Permanent
Nausea	No	Seldom	After meals	Most of the day	All the time
Vomiting	No	A few times weekly	Once daily	2-3 times every day	More than 3 times every day

before enrolment. The study was carried out according to Helsinki Declaration principles, and approval for the study was obtained from our local Ethics Committee. Each patient signed a written informed consent prior to participating in the study. Before entering the study, each patient underwent a hypersensitivity test by serial subcutaneous injections of Iscador M® (Mali) 0.1 mg, 1 mg and 3 mg on three consecutive days.

On entering the study, the time-interval between the first two punctures, without any intervention, was measured. This parameter – defined as the baseline interval (Δ_0) – was then used as an individual control for each patient. Repeated paracentesis was then performed according to the patient's needs. Following each of the subsequent abdominal punctures, 10 mg of Iscador M® (1 ml ampoule) diluted in 10-15 ml of normal saline were injected into the peritoneal cavity *via* the same catheter used for drainage. The time-intervals between the required punctures following Iscador M® administration (Δ_1, Δ_2, *etc.*) were measured and compared to the previous interval as an indicator of change in the rate of accumulation of ascitic fluid. The abdominal circumference before each drainage and the volume of fluid collected were also measured. In addition, each patient completed a symptom questionnaire before each drainage session, which was translated into a symptom score (Table I). These three parameters were then used to rule out the possibility of faulty postponement of required punctures.

Statistics. Data analysis was performed using the SPSS 11.0 statistical software. Both a paired *t*-test and Wilcoxon signed rank tests were used to compare the variables between each of the two different points of paracentesis. For ordinal variables (*e.g.*, symptom score), a paired Wilcoxon signed ranks test was used. The level of significance was 0.05. The data are presented by box-plot (Figure 1).

Results

Between February 2000 and April 2003, a total of 25 patients with end-stage malignancies of variable origins were enrolled into the study. Their main clinical characteristics are presented in Table II. The performance status of all 25 patients ranged from 3-4 and their median survival time was 1.5 months (range, 0.5-17 months). The median number of paracentesis performed per patient after entering the study was four (range, 1-8; one patient had 22 paracentesis). Two patients died 12 and 14 days following baseline puncture and were not treated with Iscador M®. Those two patients were not included in the evaluation for efficacy and toxicity. Twenty of the other 23 patients were treated and followed until death. Three patients were taken off the protocol and treated with chemotherapy for various reasons: a patient with granulosa cell tumor, because of lack of response to three consecutive intraperitoneal installations of Iscador M®; one patient with abdominal mesothelioma, the ascites being substituted by an abdominal mass after the second injection of Iscador M®; one patient with small cell lung cancer achieved prolonged intervals between consecutive punctures and became suitable for systemic therapy.

The 23 treated patients were all evaluable for response and toxicity to Iscador M®. Only 14/23 (61%) patients survived long enough to have the third installation of Iscador M® and were available for evaluation of the second interval (Δ_2). Seven patients were available for evaluation of more then two intervals with Iscador M® treatment. One patient with ovarian carcinoma had a clinical objective response represented by a reduction in CA-125 levels from 800 U/ml to 102 U/ml, and improvement in ascites accumulation and in performance status; this regression lasted for 12 months.

Data concerning the intervals between every two paracentesis for those patients evaluable for response is presented in Figure 1. The median baseline interval between

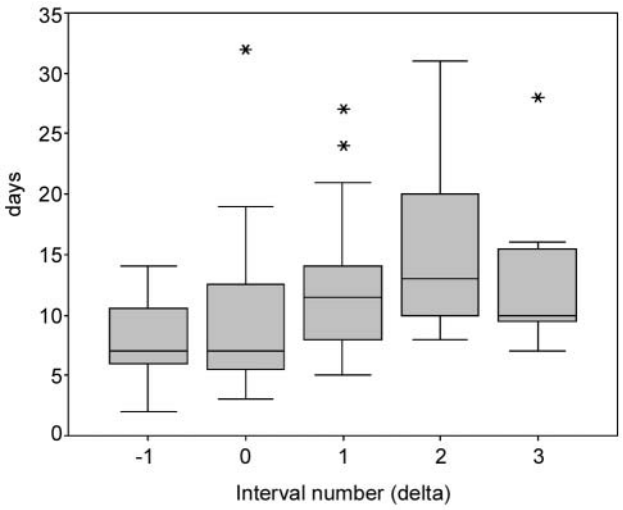

Figure 1. *Box plots of intervals between paracentesis. Solid lines express the median values; boxes the 25-75% quartile; whiskers the minimum and maximum observed values that are not outlier. Outliers (expressed by *) are single values larger than x1.5 of the box-length.*

Table II. *Characteristics of patients treated with intraperitoneal Iscador M®.*

No. of patients:	25
Age: median (range) years	64 (46-86)
Male/Female	12/13
Performance status (WHO)	
3	13
4	12
Albumin level: median (range)	2.6 g/dl (1.7-3.9 g/dl)
Histology	
Colorectal carcinoma	8
Ovarian carcinoma	8
Pancreatic carcinoma	3
Stomach carcinoma	2
Granulosa cell tumor	1
Abdominal mesothelioma	1
Small cell lung cancer	1
Carcinoma of unknown origin	1

the first two paracentesis without any intervention (Δ_0) was 7 days (range; 2-14 days; mean±SD 7.9±3.3). Following the first installation of Iscador M®, the median interval between paracentesis (Δ_1) increased to 12 days (14±9.5), based on all 23 treated patients. Prolongation of the interval was seen in 20 out of 23 patients, and shortening of the interval in three. The difference (Δ_1–Δ_0) ranged between (–6) and (+17) days, with a mean±SD value of 4.3±5.1 (95% confidence interval (CI) 2.1-6.5; p=0.001). A further increase to a median of 13 days (14.9±6.7) was observed after the second intraperitoneal installation of Iscador M® in 14 patients. Prolongation was seen in 10/14 patients, no change in one and shortening of the interval in three. The difference (Δ_2–Δ_1) ranged from (–4) to (+18) days, mean 3.6±5.6 (95% CI; 0.4-6.9; p=0.03). The nine patients who died during the Δ_2 interval and were not included in the (Δ_2–Δ_1) analysis fared as well as the 14 surviving patients concerning the effect of Iscador M® during the Δ_1 interval (median Δ_1 interval 12 and 11.5 days, respectively, p value not significant). This renders improbable the possibility of drop out bias as the cause for further improvement in the Δ_2 interval between paracentesis. Further analysis of seven patients who had more then three installations revealed stabilization of the intervals, but the sample size was too small to draw any conclusion.

Data on pre-study paracentesis (Δ_1) was available for 15 participating patients and the median interval between punctures was seven days, similar to the baseline interval (p=0.83). This validates the results concerning baseline and post-treatment intervals.

There was no difference in abdominal circumferences, volume of drained fluid and the symptom score values measured before the baseline paracentesis and before the two following ones. On entering the study, the median volume of peritoneal fluid collected by paracentesis was 5 liters (range, 1.5-9 liters). The median volume after the first and second Iscador M® installations was 4.5 liters (range, 1-9 liters) (NS). The median abdominal circumferences were 106 cm on entering the trial and 103.5 cm and 102 cm after the first and second installations, respectively. The median albumin level was 2.6 g/dl (range, 1.7-3.9 g/dl) on entering the trial.

Although no significant statistical benefit was seen in the symptom score, the Wilcoxon ranks test showed a trend to improvement after the first treatment with Iscador M® in abdominal pain (p=0.12), abdominal pressure (p=0.12) and waking up at night due to shortness of breath (p=0.09). In any event, no worsening of symptoms meant no faulty postponement.

Toxicity was negligible, and included one patient with an episode of transient abdominal pain that started 1 hour after the first installation of Iscador M® and lasted for 24 hours. No analgesic medications were required. No similar episodes were observed in that patient on the following installations of Iscador M®. No other side-effects were documented during the study.

Discussion

The management of malignant ascites includes repeated paracentesis, diuresis, or insertion of a peritoneo-venous shunt (2). A Canadian survey (12), examining physicians'

attitudes toward the management of malignant ascites, concluded that paracentesis is used by 98% of physicians and diuretics are used by 61%. Other modalities are infrequently used. Repeated paracentesis remains the mainstay of treatment for patients with malignant ascites, providing good, albeit temporary, relief of symptoms. Lymphatic obstruction has been considered the main pathophysiological mechanism causing formation of malignant ascites. Recent evidence suggests that immune modulators, vascular permeability factors and metalloproteases are significantly involved in the process (13).

The goal of this prospective study was to evaluate the clinical efficacy and toxicity of Iscador M® administered intraperitoneally as a means to reduce fluid accumulation. No attempt was made to investigate the modulator effect of this compound on the host immune system, nor was the effect on survival rate an end-point. Statistically significant prolongation of the interval between two successive paracenteses was seen after the first installation of Iscador M®. The time-interval was further prolonged after the second administration of Iscador M®. The small number of patients who survived long enough to receive the third installation of Iscador M® renders any further conclusion impossible. Similar results were reported by Mackey *et al.* (14) with intraperitoneal administration of triamcinolone hexacetanide given to 15 patients. They suggested that the effect of this corticosteroid is gained by down-regulation of the vascular endothelial growth factor (VEGF). There is no data suggesting any effect of *Viscum album* extract on VEGF.

Several biological response modifiers have been evaluated for the treatment of malignant ascites. In a case series study including 100 patients with malignant pleural, peritoneal or pericardial effusions, Lissoni *et al.* administered intracavitary low-dose interleukin-2 into the involved cavity (15). Twenty-one patients had malignant ascites. The peritoneum was the least responsive site, with a 43% response rate. In a study by Sartori *et al.* (16), 45 patients with ascites were treated with Interferon alpha-2b instilled into the peritoneal cavity. The treatment was given once every four days, six times in total, following maximal drainage of the peritoneal fluid through a fixed tube. The global response rate was 66%. The caveats of this study included the need for hospitalization for 24 days throughout the treatment, and the need to install a long-standing catheter. In a small three-arm study by Nio *et al.*, including 42 patients (17), total disappearance of ascetic fluid was achieved in 29% of patients by intraperitoneal injection of OK-432. This streptococcal preparation, when combined with intraperitoneal chemotherapy, eliminated the ascites in 43% of patients, while administration of chemotherapy alone failed to achieve any response. Analysis of the cytokine kinetics revealed a prominent increase in the level of interleukin-6 in the peritoneal fluid in the combined treatment group. These studies present some encouraging results, but none have reached the point of adoption into daily clinical practice.

Viscum album extracts were reported to enhance the production of several immune modulators, such as interleukin-1, interleukin-6 and tumor necrosis factor alpha (5, 7). Although their exact mode of action is not fully known yet, indirect effects through cytokines are possible.

It should be emphasized that our study population presented with an extremely short lifespan and impaired performance status, with a median survival of only six weeks. The rapid deterioration in the patients' conditions limited the ability to evaluate the real impact of Iscador M® administration on their quality of life. Nevertheless, no deterioration in symptoms related to ascites was observed and no toxicity to treatment was seen.

The results of the current single arm phase II study, while encouraging, are preliminary. Nevertheless, the administration of the medication was simple, with no need for hospitalization or other special procedures. Treatment with Iscador M® seems to be a feasible approach that can be applied by a home care unit and is suitable for treating patients in their last months of life.

In conclusion, the instillation of Iscador M® into the peritoneal cavity following paracentesis is an easy procedure which may reduce the need for repeated paracentesis in patients with malignant peritoneal fluid. A randomised phase III trial is indicated to confirm these results and to rule out the possibility of biased results due to the single arm phase II form of the current study.

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