A Pilot Study of Long-Acting Octreotide for Symptomatic Malignant Ascites

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Key Words

Malignant ascites · Octreotide · Paracentesis

Abstract

Background: Effective, non-invasive, palliative strategies for symptomatic malignant ascites are unavailable. This trial explored whether octreotide, an inhibitor of vascular endothelial growth factor, a putative mediator of ascites, prolongs the interval to next paracentesis. **Methods:** After a baseline paracentesis and a test of short-acting agent, patients with symptomatic ascites were randomly assigned to long-acting octreotide (Sandostatin LAR[®]) depot 30 mg intramuscularly every month versus 0.9% sodium chloride administered similarly. Patients were then monitored for recurrent, symptomatic ascites. **Results:** Thirty-three patients were enrolled: 16 assigned to the octreotide and 17 to the control arm. The median time to next paracentesis was 28 and 14 days in the octreotide and placebo arm, respectively ($p = 0.17$). After adjustment for extracted ascites volume and abdominal girth change, no statistically significant difference between the groups was observed (hazard ratio = 0.52, with a 95% confidence interval of 0.21–1.28; $p = 0.15$, per Cox model). Octreotide-treated patients described less of abdominal bloating

($p = 0.01$), abdominal discomfort ($p = 0.02$), and shortness of breath ($p = 0.007$) at one month, although other quality of life symptoms were comparable between the arms. Long-acting octreotide was reasonably well tolerated. **Conclusion:** As prescribed in this trial, octreotide did not seem effective in prolonging the time to next paracentesis, although improvements in symptoms suggest that vascular endothelial growth factor inhibition merits further investigation.

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Malignant ascites occurs in >20% of patients with ovarian, gastrointestinal, or unknown primary cancers [1]. Among ovarian cancer patients in their last year of life, ascites is one of the most frequent reasons for hospitalization [2]. Underscoring the widespread untoward ef-

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fects of malignant ascites, Mackey et al. [3] assessed 15 patients, ascribing dyspnea, nausea, abdominal pain and distension, an inability to eat as well as an overall 'unwell' feeling to a constellation of symptoms associated with ascites.

Despite the foregoing, palliative options for patients with malignant ascites and ascites-associated symptoms remain limited [4, 5]. Paracentesis appears to be the most regularly employed intervention in the United States, but it is invasive, often requires repetition every 9–10 days, and can be associated with pain, continuous leakage of peritoneal fluid from the needle site, and, very occasionally, bowel perforation. More recently, case reports and small series describe the use of more permanent catheters, but this approach is also invasive and can be uncomfortable because of the extruding catheter. Second, diuretics might at first seem a reasonable option but remain ineffective in up to 70% of cancer patients. Third, peritoneal-venous shunts or transjugular intrahepatic portosystemic shunts have been tried, but these interventions are also invasive and can lead to infections, thrombophlebitis, and dissemination of metastases. Finally, catumaxomab is a monoclonal antibody that binds to the epithelial adhesion molecule EpCAM, to the T-cell antigen CD3, and to dendritic cells, natural killer cells, and macrophages. A randomized controlled trial demonstrated a prolongation of paracentesis-free survival from 14 days in control patients to 37 days in catumaxomab-treated patients ($p < 0.001$) with similar benefits specifically in ovarian cancer patients [6]. Although these findings suggest the potential value of this agent in palliating malignant ascites, the fact that catumaxomab is administered intraperitoneally and causes side effects such as fever, nausea, vomiting, and ileus points to the need to continue to investigate less invasive, better tolerated strategies.

Thus, the current study focused on octreotide. Octreotide is a safe and relatively well-tolerated analogue of sandostatin, a natural hormone used to palliate several conditions, including bowel obstruction, diarrhea, and the symptomatology of neuroendocrine tumors. Recent studies also suggest octreotide may have inhibitory effects on vascular endothelial growth factor, a well-characterized mediator of ascites [7, 8]. Additionally, published case reports suggest that octreotide might palliate ascites [9, 10]. Building further upon such preliminary findings, this pilot study explored whether octreotide could palliate the symptoms of patients suffering from malignant ascites.

Methods

Overview

This randomized, placebo-controlled pilot study explored the effects of a long-acting octreotide preparation in patients with symptomatic ascites. All recruitment sites were part of the North Central Cancer Treatment Group, a cancer cooperative group funded by the National Cancer Institute. The Institutional Review Board of each participating institution granted approval prior to the enrollment of patients, and all patients were required to provide written consent at the time of enrollment.

Patient Population

Inclusion and exclusion criteria were well outlined in the study protocol and were adhered to throughout accrual to the trial. These inclusion criteria consisted of the following: (1) patient age of ≥ 18 years at the time of enrollment; (2) histologic or cytologic proof of malignancy other than lymphoma; (3) the treating oncologist believed current ascites was malignant; (4) therapeutic paracentesis was planned in ≤ 3 days after randomization or was completed in the 2 days prior to therapy; (5) the patient viewed ascites as problematic, and (6) the patient was willing to provide an ascites sample for research purposes, and, if it was a Mayo Clinic patient, was willing to provide a blood sample for research (results of the latter are not reported here).

Patient exclusion criteria consisted of the following: (1) history of cholecystitis with no prior cholecystectomy; (2) allergic reaction to octreotide and/or latex; (3) history of chronic renal failure with a creatinine twice the institution's upper limit of normal; (4) life expectancy of < 4 weeks; (5) pregnant or nursing or, if of child-bearing potential, unwilling to employ contraception; (6) concurrently receiving octreotide or intraperitoneal chemotherapy; (7) uncontrolled diabetes; (8) receiving warfarin or at high risk for bleeding from a procedure; (9) concurrently or about to receive first-line chemotherapy for any malignancy other than exocrine pancreas cancer; (10) concurrently receiving bevacizumab, and (11) cirrhosis or portal hypertension.

Patient Enrollment

At enrollment, all patients underwent a history and physical examination, platelet count check, a paracentesis (as per the time frame outlined above), measurement of abdominal circumference at the umbilicus prior to paracentesis, and completion of the previously validated Common Liver Disease Questionnaire [11], all of which were to be completed within ≤ 3 days after randomization. The Common Liver Disease Questionnaire was used because, in the opinion of the study team, its questions appeared clinically relevant to cancer patients with symptomatic ascites.

Study Intervention

Patients were then stratified based on whether ongoing chemotherapy was anticipated (yes vs. no), a history of paracentesis had occurred prior to enrollment (never vs. other), and the extent of prior chemotherapy (never received vs. only first-line vs. second-line vs. other).

Patients were then randomly assigned to either long-acting octreotide (Sandostatin LAR[®]) depot 30 mg intramuscularly every month (provided by Novartis Pharmaceuticals Corporation, East Hanover, N.J., USA) versus 2 ml of 0.9% sodium chloride administered in the same manner [12].

Prior to starting treatment, patients received a test dose of either 100 µg/ml of octreotide acetate or saline based on their randomization. In the event the test dose was well tolerated on day 1, patients were then to start either the long-acting formulation of octreotide or saline on day 2. Patients were to continue with monthly injections based on their assigned treatment arm.

Monitoring

Patients were monitored monthly or more frequently if they required an interim paracentesis. If a patient required a paracentesis prior to the 1-month time point, a repeat measurement of abdominal girth at the umbilicus followed by the procedure itself was undertaken. The volume of extracted ascites was recorded, and at least 10 ml of fluid was sent for assessment of vascular endothelial growth factor (VEGF) concentrations.

Monthly clinic evaluations entailed a repeat history and physical examination. The Common Terminology Criteria for Adverse Events version 3 was used for the grading of adverse events at each monthly visit with the healthcare provider. Patients completed an assessment for adverse events and the Common Liver Disease Questionnaire every 2 weeks [11].

Dose Modifications

Patients were to stop the intervention permanently in the event of grade 3 or worse diarrhea, abdominal pain, constipation, or hyperglycemia. Biliary toxicity of any grade was to be reported as an adverse event and was to prompt complete and permanent discontinuation of study treatment.

Translational Component

After the first paracentesis at enrollment and after subsequent paracenteses, 10 ml of ascites fluid was analyzed for vascular endothelial growth factor. A QuantiGlo® Chemiluminescent VEGF Immunoassay kit from R&D Systems was used to measure VEGF₁₆₅ isoform in ascites fluid. Samples were run in duplicate. This isoform was chosen as a marker to indicate proof of target interference because of its abundance and potency [13, 14].

Statistical Methods and Analyses

The primary aim of this study was to report the time to next paracentesis. This analysis required an adjustment for volume of ascites withdrawn at baseline paracentesis at study entry and for change in abdominal circumference between procedures, as it was assumed that patients who received a small-volume paracentesis at baseline might require a second one shortly thereafter. A log-rank test was used for this analysis along with a Cox proportional hazards model to adjust for baseline paracentesis volume and change in abdominal circumference. Other study aims include a comparison between arms of the number of paracenteses during the first month and the total number over the entire study. These numbers were compared with Wilcoxon nonparametric tests. Quality of life scores were summed, compared between study arms and are presented descriptively. Adverse events are also reported descriptively regardless of attribution.

For the translational component, a 50% decline in VEGF in ascites was sought between the baseline and next paracentesis. This change was based on data from Zebrowski et al. [15], where this degree of decline represents a one-half standard deviation, or a moderate effect size. Fisher's exact test was used to compare the

Table 1. Baseline demographics

	Octreotide (n = 16)	Placebo (n = 17)	p value
Age, years			
Median	62	69	0.22
Range	45–90	40–88	
Gender			
Female	10 (63)	12 (71)	0.62
Male	6 (37)	5 (29)	
Prior chemotherapy			
Never	0	1 (6)	0.68
Only first-line	6 (38)	5 (29)	
Second-line	6 (38)	8 (47)	
Other	4 (25)	3 (18)	
Cancer			
Ovarian/peritoneal	3 (19)	6 (35)	0.20
Gastrointestinal	5 (31)	1 (6)	
Other	8 (50)	10 (59)	
No paracentesis prior to enrollment	2 (13)	3 (18)	0.68

Figures in parentheses are percentages.

proportion of patients who achieved a 50% decline in VEGF levels between the two treatment arms. All inferences were performed with a 2-sided test at a 0.05 level of significance. No adjustments were made for multiple testing.

Results

Demographics

A total of 33 patients were enrolled, 16 assigned to the octreotide arm and 17 to the control arm. Slow accrual prompted early study closure that led to enrollment of slightly under half of the intended cohort of 68 patients. Patient demographic data are shown in table 1. All 33 patients tolerated the test dose of octreotide/placebo and were included for the assessment of the primary study endpoint.

Of incidental note, 8 octreotide-treated and 9 placebo-exposed patients received concurrent chemotherapy. Additionally, 9 octreotide-treated and 7 placebo-exposed patients received concurrent diuretics.

Efficacy Endpoints

The median time to next paracentesis was 28 days in the octreotide arm and 14 days in the placebo arm ($p = 0.17$, log-rank test) (fig. 1). After adjustment for volume of

Fig. 1. Time to paracentesis. The median time to first paracentesis was 28 days in the octreotide arm and 14 days in the placebo arm ($p = 0.17$).

extracted fluid and change in abdominal girth, no statistically significant difference was observed between study arms (hazard ratio = 0.52, with a 95% confidence interval of 0.21–1.28; $p = 0.15$, per Cox model).

During the first 1-month treatment cycle, the median number of paracenteses in the octreotide-treated patients was 0.5 (range 0–4); in placebo-exposed patients, it was 1 (range 0–4). The median number of paracenteses over the duration of the study for each octreotide-treated patient was 1 (range 0–17), and for placebo-exposed patients, it was 1 (range 0–7; $p = 0.68$). The median volume per paracentesis per patient was 3,400 ml (range 28.5–7,500) and 3,500 ml (range 500–7,500) among octreotide-treated and placebo-exposed patients, respectively ($p = 0.99$).

Most patients had only one injection of long-acting octreotide/placebo (81% in the octreotide arm and 77% in the placebo arm). The median number of octreotide injections was 2.9 (range 1–26), and the median number of placebo injections was 1.5 (range 1–4). The median number of days on study was 27 (range 5–731) and 29 (range 8–117) in patients in the octreotide and placebo arm, respectively ($p = 0.45$). Finally, the overall median survival was slightly >1 month and was not statistically different between arms.

Quality of Life

Scores were comparable at baseline. Although high drop-out rates and concerns for multiple comparisons invite caution in interpretation, at 1 month, placebo-exposed patients described worse abdominal bloating ($p = 0.01$), abdominal discomfort ($p = 0.02$), and shortness of breath ($p = 0.007$; table 2). Questionnaire items for fa-

tigue, pain, sleepiness, desire to eat, strength, trouble lifting, anxiety, energy, happiness, drowsiness, irritability, difficulty sleeping, impact of the disease on family members, mood swings, inability to fall asleep, muscle cramps, dry mouth, trouble concentrating, itching, and other factors were not statistically different between study arms.

VEGF Analyses

Only 7 patients were able to provide both baseline and follow-up samples for VEGF levels in ascites. Octreotide-treated patients manifested a drop from baseline of 16 pg/ml (SD 54), and placebo-controlled patients manifested an increase of 28 pg/ml (SD 40; $p = 0.29$). No patient in either arm manifested a 50% drop in VEGF concentration over time.

Adverse Events

No adverse events were reported from the octreotide/placebo test dose. The long-acting octreotide was also reasonably well tolerated with no cholecystitis in octreotide-treated patients and with only one mild event in placebo-exposed patients.

Adverse events are described regardless of attribution. Among octreotide-treated patients, 10 grade 4 events occurred among 6 patients. These events include abdominal pain, hyperkalemia, cognitive dysfunction, dehydration, neutropenia, fatigue, hypoxia, and anemia. Among placebo-exposed patients, 4 grade 4 events occurred among 3 patients. These included abdominal pain, fatigue, and hepatic failure and again are presented regardless of attribution. No patient stopped the study intervention because of drug-related adverse events.

Table 2. Select quality of life scores at 1 month

	Octreotide (n = 10)	Placebo (n = 15)	p value
‘How much of the time in the last 2 weeks have you been troubled by a feeling of abdominal bloating?’			
All of the time	1 (10)	2 (13)	0.013
Most of the time	0	5 (33)	
A good bit of the time	1 (10)	5 (33)	
Some of the time	5 (50)	2 (13)	
A little bit of the time	0	0	
Hardly any of the time	3 (30)	1 (7)	
None of the time	0	0	
‘How much of the time during the last 2 weeks has shortness of breath been a problem for you in your daily activities?’			
All of the time	0	5 (33)	0.007
Most of the time	0	2 (13)	
A good bit of the time	1 (10)	4 (27)	
Some of the time	5 (50)	1 (7)	
A little bit of the time	1 (10)	1 (7)	
Hardly any of the time	1 (10)	2 (13)	
None of the time	2 (20)	0	
‘How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal discomfort?’			
All of the time	0	3 (20)	0.023
Most of the time	1 (10)	6 (40)	
A good bit of the time	2 (20)	1 (7)	
Some of the time	2 (20)	3 (20)	
A little bit of the time	5 (50)	1 (7)	
Hardly any of the time	0	1 (7)	
None of the time	0	0	

Figures in parentheses are percentages. Selection is based on statistically significant differences between the arms. Percentages may not sum to 100 because of rounding.

Discussion

This study explored whether long-acting octreotide provides palliation to patients with symptomatic malignant ascites. Based on the results of the primary analysis and the other findings reported here, we are unable to conclude that long-acting octreotide is an agent of value in palliating malignant ascites. However, early study closure after accrual of less than half of the intended sample size and enrollment of patients with a very short expectancy preclude definitive conclusions. In effect, we view this study as tentatively but not conclusively negative.

Nonetheless, the findings from this study remain intriguing from the standpoint of indicating a need to further test VEGF inhibition for the palliation of malignant

ascites. Specifically, we observed that, although statistical significance was not attained, the interval between paracenteses was twice as long with octreotide, that 1 patient in the octreotide arm remained on study for as long as 731 days without a paracentesis, that 1-month symptoms of abdominal discomfort, abdominal bloating, and shortness of breath were less among octreotide-treated patients, and that, although only meager translational data were available, such data were consistent with the inhibition of octreotide of circulating VEGF. Hence, such preliminary findings suggest that strategies to block VEGF merit further study in an effort to palliate ascites and its associated symptoms.

Of perhaps equal importance, the current study highlights the morbidity and mortality associated with malignant ascites in patients approaching the end of life. Patients in both study arms suffered adverse events that were not directly attributable to either the octreotide or placebo intervention. These events/symptoms included abdominal pain, cognitive dysfunction, dehydration, and fatigue. Patient-reported outcomes, according to the Common Liver Disease Questionnaire, indicate that nearly all patients in both study arms suffered from abdominal bloating, shortness of breath, and abdominal discomfort. Moreover, the median survival within this cohort was only slightly >1 month. Thus, although this study does not demonstrate the efficacy of octreotide in controlling ascites-related symptoms, it does underscore that such difficult symptoms are highly prevalent among patients with malignant ascites and that effective palliation is needed.

Given the slow accrual of the current trial, is it reasonable to pursue further studies to palliate patients with malignant ascites? For all the reasons outlined earlier – that ascites is common and that patients are plagued with a variety of troubling ascites-associated symptoms – we believe it is. Perhaps a modification of the study design might have enhanced accrual. First, liberalizing the eligibility criteria of this study might have led to more expeditious and complete recruitment of the intended sample size. Indeed, in retrospect, the eligibility criteria for the current study were perhaps too restrictive. This study precluded enrollment of patients receiving first-line chemotherapy, even though ascites-associated symptoms among these patients are likely also highly problematic and these patients with a longer life expectancy could well benefit from an effective palliative intervention. Similarly, patients thought to be at high risk of bleeding were also excluded, although previous reports indicate that a paracentesis can be conducted safely under such circumstances [16]. To ensure that a large and representative sample

of patients with malignant ascites is enrolled, future studies might focus on incorporating eligibility criteria that are less restrictive. Second, the possibility that patients could potentially be assigned to a placebo arm might also have diminished the enthusiasm for recruiting patients to this trial [17]. When the current study was first conceived, bevacizumab was less widely used and the data with catumaxomab for ascites palliation had not yet been published. The advent of these interventions might allow future studies to incorporate one of these agents and allow for a comparative study design that would bypass a placebo arm.

In conclusion, this study provides further evidence that ascites is highly problematic for cancer patients. It

also underscores the importance of testing safe and less invasive interventions to palliate the symptomatology associated with ascites.

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