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Targeting and Palliating Malignant Ascites: An Overview of an Upcoming Clinical Trial from the North Central Cancer Treatment Group

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Introduction

Ascites is common in patients with cancer and leads to morbidity. Ten to fifteen percent of patients with gastrointestinal malignancies and 20% of patients with carcinomas of unknown primary develop symptomatic ascites at some point during their disease course.[1,2] Although ovarian cancer represents only 2% of all malignancies,[3] patients with this malignancy are over-represented in such series of patients with ascites. Inexplicably, patients with ovarian cancer constitute 20% of all cancer patients with ascites.[1,2]

Ascites refers to a progressive accumulation of fluid within the abdomen. When extreme, it displaces organs and distends the abdominal wall, thereby causing an array of symptoms that includes an "unwell" feeling, nausea, pain, dyspnea, inability to eat, abdominal distension, and a negative self-perception.[2,4] Von Gruenigen and colleagues observed that in the last 12 months of life, symptomatic ascites constitutes 1 of the 3 most frequent reasons for hospitalization for patients with ovarian cancer (bowel obstruction and pleural effusion being the other 2).[5] Such morbidity leaves no question that ascites represents a major problem for many patients with cancer.

How is ascites palliated? Lee and colleagues surveyed 80 randomly chosen physicians who see patients with malignant ascites.[6] Ninety-eight percent described paracentesis as the most common intervention, yet the procedure is invasive, can be painful, can require repetition as frequently as every 9-10 days,[2] and carries serious complication rates as high as 24%, including, on rare occasion, bowel perforation. To quote physicians directly, ascites is "generally impossible to manage" and represents "a frustrating clinical situation."[6] Such statements suggest a dearth of effective palliative strategies. Diuretics are ineffective in approximately 70% of patients with cancer.[7] Peritoneal-venous shunts are sometimes used but can lead to infection, thrombophlebitis, intraperitoneal bowel obstruction, as well as risk of abrupt, widespread dissemination of cancer cells.[8] Although no studies have examined implanted external catheters in patients with cancer, this approach is also invasive and puts patients at risk for cellulitis/peritonitis,[9] a complication that is untenable for many patients with cancer. Finally, transjugular intrahepatic portosystemic shunts have also not been well studied in patients with cancer; however, they too are highly invasive and often malfunction.[10] Thus, these suboptimal strategies highlight the justification for this study: patients with cancer with symptomatic ascites need a noninvasive palliative intervention, and this study is aimed at meeting this need.

Previous studies have delineated the pathophysiology of malignant ascites and suggest palliative targets. Reporting on a seminal observation, Garrison and colleagues found that the instillation of cell-free malignant ascites into the peritoneal cavity of a rodent resulted in rapid accumulation of ascites far in excess of the volume instilled.[11] The concept of vascular permeability as a major cause of ascites has since gained further substantiation. Fifty thousand times more potent than hista-

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mine in causing vascular leak, vascular endothelial growth factor (VEGF) is a major mediator of vascular permeability,[12] and cancer patients with malignant ascites have very high concentrations of VEGF in their ascites.[13] Animal studies have demonstrated attenuation of ascites when a receptor decoy against VEGF was administered.[14]

Intriguing but anecdotal clinical evidence also suggests a potential palliative role for VEGF blockade. Octreotide is a somatostatin analogue commonly used in carcinoid syndrome, diarrhea, and variceal bleeding, and it appears to diminish VEGF tumor expression.[15-21] Particularly relevant is a recent report by Cairns and Malone that includes 3 patients with malignant, symptomatic ascites: 1 with colon cancer, 1 with an adenocarcinoma of unknown primary, and the third with breast cancer.[22] The first patient received octreotide as part of bowel obstruction management and experienced complete resolution of ascites. The other 2 patients were given octreotide, and both manifested a decrease in ascites, with the patient with breast cancer requiring no further paracenteses. These findings are anecdotal, and the duration of follow-up is not clearly described, but this report draws attention to the only noninvasive, potentially effective clinical therapy for symptomatic ascites and invites further study of this intervention as a palliative strategy.

Finally, can we better predict who will develop symptomatic ascites and who might be more likely to benefit from an intervention such as VEGF blockade? Two prevalent polymorphic sequences of the *VEGF* gene appear to modulate circulating VEGF concentrations and might predict ascites development in patients with cancer. First, Renner and colleagues found that 16% of 119 healthy individuals had a C→T exchange at position 936 of exon 8 in the *VEGF* gene, referred to herein as the 936 C/T polymorphism of the *VEGF* gene.[23] In a subgroup analysis, these investigators observed that 7 individuals with the 936 C/T polymorphism had significantly lower VEGF plasma concentrations compared with 16 individuals with other genotypes. Other investigators, including Livingston and colleagues, have also found that this polymorphism is associated with decreased circulating VEGF.[24] Secondly, the −634 C/G polymorphism is located in the 5'-untranslated region of the *VEGF* gene. Awata and colleagues found a 46% frequency of this allele in a general Japanese population; in an unspecified but mixed ethnic population, this frequency was reported to be 30%.[25] Awata and colleagues found that this allele is associated with significantly higher serum VEGF concentration among 11 healthy subjects with this polymorphism compared with 53 other individuals with other genotypes (P = 0.02). Although the allelic and genotype frequencies of each of these polymorphisms are known in these limited populations, their frequencies have not been determined in patients with ovarian cancer. Because previous studies in other cancer types, such as lung cancer and breast cancer, suggest these polymorphisms might be associated with greater cancer risk, it is important to estimate prevalence rates in cancer patients with ascites and not to infer rates from previous observations from limited populations.[26,27] The possibility of testing for these polymorphisms in the current trial could allow us to develop stratification factors that might be used in future palliative trials for ascites.

Trial Design

A dearth of trials aimed at palliating symptomatic ascites requires that a placebo-controlled trial be conducted in order to gain a better understanding of the natural longitudinal history of ascites and to provide a comparative arm against which to assess the unbiased efficacy of an agent such as octreotide. In addition, anticipated high dropout rates necessitate that the primary endpoint not require that a large percentage of the cohort reach a certain time point. Hence, time to next paracentesis seems a reasonable primary endpoint, in part also because the goal of octreotide is to obviate the need for a repeat and potentially morbid procedure. Thus, although the present study is considered a pilot trial, the inclusion of a blinded placebo is justified.

In deciding to use time to paracentesis as the primary endpoint in this study, the investigative team was well aware that the long-acting sandostatin injection can take as long as 2 weeks to result in steady-state levels of octreotide.[28] However, it is important to point out that octreotide levels definitely do not remain low and flat during this 2-week period and that the amount of octreotide necessary to suppress VEGF and assuage ascites is completely unknown. Nonetheless, in the event that positive findings are not observed with respect to the primary endpoint and in the event that octreotide does appear to palliate ascites in this setting, the secondary endpoints in this trial are likely to show evidence of activity.

These secondary endpoints include the following: (1) whether octreotide will reduce the total number of paracenteses; (2) whether octreotide will reduce VEGF ascites concentrations; (3) whether octreotide is well tolerated; and (4) quality of life in both treatment arms, as assessed by a previously validated questionnaire.

Patient Characteristics and Eligibility Criteria

Perhaps one of the most frustrating aspects of a palliative trial from the standpoint of the patient and health care provider are byzantine eligibility criteria. The present study was designed to sidestep such frustration. Relevant eligibility criteria therefore include the following (Table 1): (1) patient must be ≥ 18 years of age; (2) there must be proof of malignancy (except lymphoma); (3) treating oncologist thinks that ascites is caused by cancer (positive cytology is not necessary); (4) therapeutic paracentesis must be planned ≤ 3 days after