Palliation of Symptomatic Malignant Ascites: An (Often) Unmet Need

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It is appropriate to describe the last decade in oncology as being characterized by the development of increasingly rationally developed therapeutic strategies designed to impact well-defined molecular targets. These therapies have been shown in many malignant settings to impact the time-to-disease progression and overall survival.

Unfortunately, it is also the case in most solid tumors that while treatment of metastatic disease has favorably influenced outcome, ultimate progression of the disease process is the rule rather than the exception. As a result, it is critical that the oncology research community continues to aggressively explore strategies to effectively palliate cancer-related symptoms and to optimize the quality-of-life for individuals experiencing progressive cancer.

Consider, for example, the management of malignant ascites. This relatively common condition in the natural history of patients with cancers of the ovary and gastrointestinal tract can result in considerable physical distress and may quite negatively impact an individual's functional abilities during the remaining months of her/his life.

And while the performance of a paracentesis can result in rather immediate short-term improvement in abdominal discomfort and in the ability of many individuals to both eat and increase their daily-life activities, the distress will often rapidly recur, necessitating frequent procedures. Moreover, protein depletion associated with

the removal of malignant ascites may exacerbate and potentially accelerate the debilitating process of cancer cachexia. Unfortunately, in the presence of chemotherapy-resistant malignant disease involving the peritoneal cavity, which results in the formation of ascites, there is little to offer patients other than intermittent (and often frequent) fluid removal. Thus, strategies to favorably impact this clinical state are urgently needed.

In this issue of *Oncology*, investigators from the Mayo Clinic report a provocative experience with long-acting octreotide in the management of malignant ascites [1]. The investigators must be complimented on the rational approach they employed for their evaluation. Use of a randomized phase-2-trial design permitted the establishment of a reasonable baseline (or 'control' group) for the overall patient population with malignant ascites at their center who would be candidates for treatment for this complication of progressive malignant disease.

The data clearly demonstrate the seriousness of the clinical problem with the 'control group' (n = 17 patients) needing a paracentesis in a median time of only 14 days following their most recent prior procedure [1].

Of interest, treatment on the experimental arm (n = 16 patients) appeared to be associated with an improved time to the requirement for a paracentesis (median 28 days), but by the prospectively-defined endpoint this delay did not achieve 'statistical significance' (p = 0.17). As a result, the investigators labeled this a negative result/

outcome, stating ‘octreotide did not seem effective in prolonging the time to next paracentesis’ [1].

This is certainly not an incorrect conclusion, especially considering the cost of the specific approach examined in this study. However, it is the opinion of this commentator that one can legitimately question whether it is really necessary to demonstrate such a high degree of statistical significance ($p < 0.05$) in a setting where the fundamental goal of the research is to determine if there is a reasonable chance of a strategy providing a meaningful level of direct clinical benefit, either by favorably impacting a particular symptom or influencing the overall quality of life. Under these circumstances, what is wrong with accepting a statistically-defined risk of a false-positive result of 1 in 10 or even 1 in 5?

Or perhaps patients with these particular symptoms who are asked to participate in this type of trial might be directly asked what level of certainty would they personally require before they would accept the argument that the specific approach has a reasonable chance of being ‘beneficial’ in improving their symptoms? Is it not ratio-

nal to argue that the collective opinion of patients on the subject is as relevant as that of the statistician?

And if a modified level of ‘statistical proof’ was ultimately deemed acceptable for suggesting (‘defining’) clinical benefit in relatively small, but unquestionably well-designed and conducted randomized studies like the Mayo Clinic trial, which examine novel approaches to palliate progressive cancer-related symptoms, it is possible that many more such efforts would be undertaken by investigators and industry sponsors. Finally, it is reasonable to argue that such efforts might eventually lead to the development of more effective strategies in these clinical settings.

And would that not be a very ‘positive’ outcome?

Reference

- 1 Jatoi A, Nieva JJ, Qin R, Loprinzi CL, Wos EJ, Novotny PJ, Moore DF Jr, Mowat RB, Bechar N, Pajon ER Jr, Hartmann LC: A pilot study of long-acting octreotide for symptomatic malignant ascites. *Oncology* 2012;82:315–320.