Editorial

Circulating tumor cells in biliary cancer: First step or false step?

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Cholangiocarcinoma and gallbladder cancer are uncommon malignancies which are notoriously difficult to diagnose and treat, and for which surgery is the only curative treatment (1,2). Improvements in systemic therapy has been plodding, due to the difficulties in trial design posed by the study of uncommon tumors, a lack of available active agents for treating these diseases, and an inadequate understanding of the biology of these malignancies.

Ustwani and colleagues in the current issue of the Journal of GI Oncology report the results of their investigation of the incidence and implications of detectable CTCs in patients with advanced biliary cancer (3). Assays were performed serially in 16 patients, 13 with cholangiocarcinoma and 3 with gallbladder cancer. Three of 13 patients with cholangiocarcinoma and one of the 3 with gallbladder cancer were found to have 2 or more CTC's per 7.5 mL of blood at baseline. All of the patients with detectable CTCs had Stage III or IV disease, while 0/3 patients with Stage I-II disease had detectable CTCs. While a statistically significant difference in survival between patients with elevated CTCs and patients without elevated CTCs could not be demonstrated in this small pilot study, only one of the 4 patients with elevated CTCs as compared to 6 of the 12 without elevated CTCs were alive twelve months after the baseline blood draw. These data suggest the possibility that CTCs could have important prognostic significance in biliary cancer, as has been demonstrated in patients with breast, colon, and prostate cancer (4-7). This is a pilot study, so one must be careful not to make too much of the data. But these results are of interest for a number of reasons, and imply a course of future research.

The presence of detectable circulating tumor cells could indicate the presence of disease, aiding diagnosis, and a decline over time could represent a response to therapy. The simple ability to assess the effects of treatment on an individual patient's tumor would represent a significant advance in the management of biliary system tumors. An embarrassing truth is that we oncologists often have difficulty in telling whether our patients are getting better or worse with treatment. Serial radiologic studies are poorly reproducible in lung cancer and other tumors that seem to produce "measurable" disease, with discordance rates between radiologists assessing response *vs.* no response in the range of 15-20% or more (4,8,9). In the case of biliary cancers, the situation is likely worse, with few patients having easily measurable disease. While newer imaging modalities such as MRI or PET scanning may prove helpful in diagnosis, assessing the response to therapy of a patient with biliary cancer remains a challenge (1,2,10). In breast cancer and prostate cancer, the serial assessment of CTCs is superior to imaging or PSA determination, respectively, in predicting patient outcome (4,6). The ability to reproducibly and rapidly assess the response to treatment of a patient with biliary cancer would aid drug development by allowing accurate assessment of the effects of novel agents. Moreover, if "drugable targets" for biliary cancers can be identified, the ability to serially assess the expression and modulation by therapy of these targets would represent a useful tool for understanding the biology and improving the treatment of these tumors. While the ability to interrogate circulating tumor cells is at present limited, preliminary studies have indicated, for instance, that HER2 expression can be assayed in the CTCs of patients with breast cancer, and can lead to novel insights (11,12).

The possibilities discussed in the paragraph above are intriguing, but how do we get from here to there? First, the

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optimal cut-off for the number of circulating tumor cells associated with a poor outcome needs to be established. For breast and prostate cancer, this number has been determined to be more than 5 CTCs per 7.5 mL of blood (5,7). For colorectal cancer, this number has been determined to be greater than 2 CTCs per 7.5 mL tube of blood (6). Ustwani and colleagues chose the lower number, but this pilot study is not sufficiently robust to determine the optimal cutoff number, and additional studies will need to be done.

The observation of a trend for a worse survival in the patients with higher CTC numbers suggest that CTCs may prove to be a useful prognostic marker as it is for breast, lung, and colorectal cancer, but again additional, larger studies are needed to establish this possibility. Any larger study should also incorporate serial CTC assays to determine whether a decline in CTC numbers is associated with an improvement in prognosis, as has been observed in other malignancies. The need for larger studies in an uncommon disease implies that multi-institutional studies need to be performed, and the GI Oncology community needs to recognize and embrace this fact.

Finally, it is worth noting that, while the technology used by Ustwani and colleagues has received regulatory approval for clinical use in patients with breast, prostate, and colon cancer, and is the only reproducibly validated assay methodology, a variety of new technologies are being developed to investigate circulating tumor cells. Some of these new methods are similar to the Cell Search assay in that they rely on the expression of epithelial antigens (12), but others are based on physical, or other characteristics of tumor cells (13). Investigators must be aware of these newer technologies, and it is quite possible that the optimal method for CTC determination will vary with tumor type and situation.

So what can we make of the role of CTCs in biliary cancer? At present, little, other than the important observation that they can be detected in this group of diseases. But if the proverbial journey of a one thousand miles begins with a single step, that step has been taken, and that step has implied a path that needs to be followed.

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