

EDITORIAL

Circulating CD133: A Promising Biomarker, but What Are We Measuring?

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Effective biomarkers should predict outcome in a way that has significant impact on treatment recommendations; however, in the treatment of malignancies, such biomarkers have proven elusive. This is particularly true for biomarkers predicting outcome after hepatic resection in resectable metastatic colorectal cancer. While many clinical scoring systems that use pathologic and clinical characteristics may be used to stratify patients into groups with different survival rates, it is rare that these systems are able to identify subgroups with such poor survival that we probably should not be operating on them.

At our institution, the clinical risk score (CRS) has been used for many years and is a reasonably good predictor of outcome. Unfortunately, a high CRS does not preclude the possibility of long-term survival or cure and in reality does not greatly affect treatment recommendations.¹ While the degree of differential survival predicted by the CRS may be useful for devising neoadjuvant chemotherapy strategies, in reality, patients with resectable hepatic metastases are often exposed to extensive chemotherapy before and after surgery, regardless of their risk status. Furthermore, neoadjuvant treatment consisting of modern chemotherapy, especially in “high-risk” patients, has not been shown to be an effective strategy since most respond, very few progress, and there are no differences in survival rates.² To make things worse, there are numerous CRS systems and they have not universally proven to be reliable predictors of outcome across institutions, further limiting their utility.³ Even the paradigm of excluding patients with extrahepatic disease from resection has been recently challenged, since a well-selected subset of these patients experience long-term survival following resection.⁴

By contrast, some very effective predictors of outcome do exist. For example, patients with gallbladder cancer and jaundice are rarely resectable, and in our experience, all patients die of their disease within 2 years—a very strong argument against resection indeed.⁵ A second example is tumor k-ras mutation status and the use of cetuximab in the treatment of metastatic colorectal cancer. A recent prospective trial demonstrated that patients with mutated k-ras derive no benefit from this chemotherapy; we can therefore spare these patients from what we know will be a completely ineffective therapy.⁶

In this edition of the *Annals of Surgical Oncology*, Pierluigi et al. retrospectively evaluated prospectively collected preoperative peripheral blood for circulating biomarkers in patients undergoing complete resection of metastatic colorectal cancer to the liver.⁷ Seven genes were analyzed, chosen for their known expression on epithelial and/or malignant cells and their role in malignancy. Ultimately, after controlling for clinical factors with the CRS in a multivariable model, the expression of CD133 was determined to be the only independent predictor of survival. Perhaps most important, patients with high CD133 expression did very poorly—so poorly, in fact, that if the results were validated, one would have to consider alternative therapies in this patient group. With a median follow-up time of 36 months (for the whole cohort), there were no 4-year survivors in the group of patients with high CD133 expression in the peripheral blood. Simply put, expression of CD133 in the peripheral blood is a very promising biomarker for patients with resectable hepatic metastases.

Of course, these data require close scrutiny. There are some interesting aspects to this study. First, in an era of effective chemotherapy, the patients included in this study were exposed to very little. No patient received adjuvant chemotherapy and less than one-half received preoperative therapy. Second, only 44% of patients had a preoperative

staging computed tomography scan, leaving the true extent of disease in these patients unclear. On the other hand, these patients appeared to have limited hepatic disease at exploration, with no positive margins and generally low CRSs. While viewing these data in this context does not invalidate them, it raises questions about their generalizability. The genes were assayed by real-time PCR and quantified according to genes from a patient selected as the “calibrator.” Ultimately, when CD133 expression was analyzed specifically, high and low values were assigned according to the median expression number within this cohort. Therefore, the expression levels are relative to the patient population studied, raising the further question of how these levels of expression would perform as predictors in different patient populations at different institutions.

Circulating CD133 expression, at least in this preliminary analysis, appears to be quite a promising biomarker, but what is CD133 and what were the authors really measuring? CD133 is a transmembrane protein originally described on hematopoietic stem cells, as well as embryonic epithelial cells. It has also been found on endothelial and lymphangiogenic progenitors. There has been much confusion over whether CD133 expression is specific for adult organ stem cells and/or cancer stem cells. A recent study demonstrated that CD133 expression is not restricted to stem cells and is expressed on differentiated colonic epithelial cells in adult humans and mice. Furthermore, while many have believed that CD133-expressing cancer stem cells are the only population capable of tumor initiation, a recent study challenged this assumption by showing that both CD133 + and CD133 – colon cancer cells were tumorigenic in xenografts.⁸ Suffice it to say, there is much to be learned about cancer stem cells, cancer initiation and progression, and the expression of cell surface CD133.

In the end, we are left with what most provocative studies leave us: more questions than answers. Nonetheless, the authors may have hit a “home run” in preliminarily identifying a group of patients who could have a poor prognosis after hepatic resection for metastatic

colorectal cancer—a prognosis poor enough to call into question the wisdom of operating at all. Of course, there is much work to be done before such a conclusion can be made. Confirming these results in larger cohorts, prospectively, across multiple institutions and laboratories, and with clearer definitions of high and low expression must be done before a true biomarker is born. Mechanistic studies coordinated between clinicians and basic scientists to elucidate the meaning of circulating CD133 are also worthwhile. I think we have some inspiration to get to work.

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