

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Colorectal Cancer In Focus

The Significance of Circulating Tumor Cells as Prognostic Markers for Colon Cancer

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H&O Why did you look into circulating tumor cells as potential prognostic markers?

NM With the advancement of separation technology, we are now able to isolate, enumerate, and characterize circulating tumor cells (CTCs) in epithelial malignancies, and it is known that CTCs are present in the circulation of many cancer patients but are very rare in healthy people.

In a pilot study that we had previously conducted, we noticed that patients with disease progression had greater increases in CTC number than did nonprogressors.¹ Also, CTC number is a known independent predictor of progression-free survival (PFS) and overall survival (OS) in breast cancer.² Therefore, we were interested to see if it was so in patients with metastatic colorectal cancer.

H&O What was the purpose of your study and what were the results?

NM The prospective study that we conducted asked the question of whether CTCs could predict prognosis in patients with metastatic colorectal cancer. The motive behind this study was that, as treatment options expand for metastatic colorectal cancer, a blood marker with a prognostic and predictive role could potentially guide treatment.

The study, which took place in 55 clinical centers throughout the United States, the Netherlands, and the

United Kingdom, included patients who were undergoing first-, second-, or third-line therapy for colorectal cancer. All patients had an Eastern Cooperative Oncology Group performance status score of 0–2 and hemoglobin of at least 8 g/dL. We collected peripheral blood for CTC evaluation before the initiation of therapy (baseline) and at 1–2, 3–5, 6–12, and 13–20 weeks after treatment initiation. CTCs were defined as EpCAM isolated intact cells staining positive for cytokeratin and negative for CD45.

Among the approximately 400 patients who took part in this study, we found a clear difference in both PFS and OS between patients who had less than 3 CTCs in a tube of blood (7.5 mL) and those patients who had 3 or more CTCs. The difference between the 2 groups was dramatic: those who had 3 CTCs or more per 7.5 mL of blood had a median PFS of 4.5 months, whereas that of patients who less than 3 CTCs per 7.5 mL of blood was 7.9 months. Median OS in these 2 groups was 9.4 months and 18.5 months, respectively. We concluded that CTCs can serve as a prognostic factor for patients with metastatic colorectal cancer.³

H&O Were there differences in results for certain subgroups?

NM In the study, we looked at different types of treatment—whether it was first- or second-line and other

characteristics. However, we found that CTCs remained a very strong predictor of prognosis in spite of the lines or types of therapy. All subgroups had the same type of results, and there were no patient types where CTCs were not thought to be prognostic.

H&O How is this a benefit to patients, compared with existing markers?

NM One of the things we observed in the study that was quite provocative is that when we measured CTCs shortly after initiating therapy, we found that those people who continued to have high levels of CTCs a few weeks after starting therapy had a particularly poor prognosis. This raised the question of whether we can use CTCs to change therapy early on in the treatment course if the current strategy is destined to fail. This hypothesis requires additional study, but our clinical trial suggested the possibility that an early assessment before obtaining a computed axial tomography (CAT) scan might be useful in sparing patients from additional therapy that will most likely not be effective.

Moreover, in our study, we conducted a multivariate analysis that looked at a variety of clinical characteristics (eg, age, performance status) as well as CTCs in determining prognosis. Currently, performance status is the only universally recognized and validated prognostic factor; however, surprisingly, our study found that CTCs were the strongest predictor of patient outcome among all of the other prognostic variables.

Although further investigation is warranted, CTCs could potentially play a role in identifying patients who can afford prolonged treatment breaks or a reduction in treatment intensity as opposed to those who need to resume therapy more quickly. Also, the phenotyping of CTCs could lead to the selection of patients for certain targeted therapies.

H&O What are the strategies to count CTCs?

NM There are a number of different laboratory modalities that have been used to identify cells in the blood.

Scientists have looked at separating cells based on size or density or measured circulating levels of DNA in blood as a proxy for CTCs. Immunomagnetic separation techniques have been widely studied. A new technology that is being explored is the use of a microfluidic approach by flowing blood slowly over a small chip that has posts on it that are immunologically tagged to attract tumor cells. That said, despite all these methods, the only commercially available and validated technology at this point is the CellSearch immunomagnetic separation technology, which is what we used in our study.

H&O How cost effective would it be if we made counting CTCs a routine practice?

NM I think that is an open but important question, as we consider the potential benefits of any new diagnostic tests. Further study is certainly required to both better define the role of CTCs in routine patient management as well as its cost effectiveness.

H&O Counting CTCs—should this be seen as an adjunct or a replacement for other imaging techniques?

NM One of the Holy Grails would be to find a non-invasive test that could spare patients more invasive or more expensive procedures. At this point, further clinical trials would be required to define the circumstances under which one could either skip or omit CAT scans or other imaging tests on the basis of the CTC assay.

References

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