

Are Circulating Tumor Cells a New, Valid Prognostic Marker in Neuroendocrine Tumors?

TO THE EDITOR: Khan et al¹ recently reported the results of a prospective trial assessing the prognostic role of circulating tumor cells (CTCs) in neuroendocrine tumors (NETs). CTC enumeration could represent an intriguing method to define the prognosis of patients affected by NETs and to predict benefit from treatments. Khan et al¹ prospectively recruited 175 patients who were affected by NETs and measured CTCs using the CellSearch system (Veridex, Raritan, NJ), which is the only such system approved by the US Food and Drug Administration. The authors found that patients with one or more CTCs had a worse prognosis than those with less than one CTC per 7.5 mL of blood. They concluded that CTCs represent a promising prognostic marker for patients with NETs.

Nevertheless, we would like to analyze some controversial issues that emerge from this trial. The main topic of our discussion is that patients who were enrolled onto this trial were quite heterogeneous with respect to several clinical features, as described below.

First, as pointed out by the authors, the patients were affected by metastatic NETs with different sites of origin, including pancreatic, midgut, hindgut, bronchial, and unknown primary site NETs. This represents a strong limitation of the study because NETs with different primary site are characterized by distinct biologic features and clinical behavior.

Second, patients were greatly heterogeneous with respect to previously received treatments; different treatments included surgery of primary, somatostatin analogues (SSTs), chemotherapy, transarterial embolization, peptide radio receptor therapy, interferons, and liver metastasis resection. This could represent a limitation of the trial, given that we can assume that the CTC count can be influenced by the amount and type of previous treatments.

Third, in the trial by Khan et al,¹ patients who had undergone systemic anticancer therapy or embolization within the previous 2 months were excluded because these therapeutic options influence the CTC enumeration in other tumors.²⁻⁴ Nevertheless, long-term SSTs were permitted, and 70 patients (40%) were receiving SSTs at the time of the CTC count. We believe that SSTs should be considered a systemic antiproliferative treatment, as are other anticancer therapies. The antiproliferative effect of SSTs was demonstrated in the PROMID (Placebo Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors) study,⁵ in which SSTs significantly improved time to tumor progression compared with the placebo (14.3 v 6 months) in patients with functionally active and inactive metastatic midgut NETs. This effect was particularly pronounced in patients with a low hepatic tumor burden. In the trial by Khan et al, patients with midgut NETs represented the vast majority (n = 101), and approximately half of

them (n = 48) had a burden of liver metastasis of 25% or less. Therefore, SSTs in these patients could have had an antiproliferative effect that positively influenced time to tumor progression and also CTC number, just as other mentioned systemic treatments are supposed to do.²⁻⁴

Fourth, the time elapsed between the last anticancer therapy and the CTC sampling was heterogeneous as well. The median time was 20 months, with a wide range of 5 to 44 months. Moreover, we can speculate that patients with significantly different prognoses were accrued in this trial. In fact, those who did not receive any anticancer therapy for several months or even years before the CTC count represent a selected population of good-prognosis patients by default.

Finally, the authors did not preplan the timing of CTC enumeration. In other trials that have investigated the prognostic role of CTCs, CTC number was analyzed at prespecified time points^{2,6}: at the beginning of a new line of treatment and at subsequent predefined time points determined by investigator choice (ie, at first tumor assessment or at disease progression). We believe that CTC count varies depending on the timing of the blood sample collection, given that CTC number is an ideal biomarker that reflects an evolving neoplastic disease and probably the effectiveness of anticancer drugs. Therefore, we believe that CTC enumeration should be performed at preplanned time points in the course of the disease and at specific intervals before or after the anticancer treatment to obtain a significant, comparable, and reproducible value.

In conclusion, this trial represents an important research effort in the field of NETs, but we are still far from knowing the real clinical significance of CTCs in NETs, and more progress needs to be made, as was the case for breast, colon, and prostate cancer.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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