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Tumor burden and response to therapy are presently assessed by the Response Evaluation Criteria In Solid Tumors (RECIST), a standardized method for determining therapeutic response to anticancer therapy using imaging-driven measurements of lesion size. This is often accompanied by blood-based test of protein biomarkers, such as CEA in colorectal cancer and CA125 in ovarian cancers [1, 2].

The introduction of RECIST in clinical trials and daily clinical practice represented an historical step forward when it was implemented almost two decades ago [3]. More recently, advances in anti-cancer therapies and biological understanding of cancer have highlighted limitations of RECIST to assess drug response and sparked the pursuit of new methodologies to measure tumor burden. New standards are already being used in certain settings such as PET-TC to assess response in lymphoma, modified RECIST criteria in gastrointestinal stromal tumors, immunological criteria for immunotherapy or morphological response for antiangiogenic drugs [4-6]. In essence, what clinicians and patients seek is a method to assess whether drug administration is effective on tumor cells, how long it takes to do so and when it stops working. In addition, it would be preferable to continuously monitor therapeutic response, rather than wait for imaging assessments that are performed several weeks (sometimes months) after initiation of therapy.

In the current issue, Tie et al explore the potential of circulating tumor DNA in evaluating tumour burden and monitoring/predicting response to chemotherapy at an early stage of treatment [7]. Their study is based on previous evidences that tumor-derived DNA is shed into the bloodstream by cancer cell [8]. Although the presence of circulating tumor DNA in the blood of patients has been known for decades, only recent advances in genomics allowed the detection and quantification of cancer-related molecular alterations with high specificity and sensitivity [9, 10].

Using colorectal cancer as a model system, the study started by identifying tumor-specific somatic variants (mutations) in tissue specimens obtained at diagnosis, and exploiting these to monitor tumor burden non-invasively in the blood. The authors sequenced a panel of 15 genes frequently mutated in mCRC, and at least one mutation was identified in the tumor tissue of 98% of the cases. The study shows a sensitivity of basal ctDNA detection as high as 92%, and a close correlation between ctDNA quantification and initial tumor burden assessed by CT-scan. Next, the authors analysed outlier patients in which ctDNA did not correlate with tumor burden as assessed by RECIST criteria. They found a false positive and a false negative case, in which CT-scan failed to truly express the real load of the tumor. This evidence, albeit limited to a few cases, suggests that ctDNA may prove superior to RECIST criteria when it comes to assess tumor burden. The study also confirms earlier observations that ctDNA is superior to CEA as a blood marker of tumor load. This is likely due to fact that somatic genomic variants in oncogenes and tumor suppressor genes are tumor-specific and to the fact that ctDNA has a shorter half-life than CEA.

Up until this point the findings are not novel, as previous studies have highlighted that somatic mutations can be used to monitor tumour burden in colorectal and other cancer types [8, 11]. Rapid increases in ctDNA levels are also known to correlate with disease progression and declines in ctDNA levels with successful pharmacological or surgical treatment [11-14].

The innovative section and the central finding of the current report is the evidence that the modulation of cancer mutations levels in circulating free DNA appears to anticipate response to therapy assessed by the classical RECIST criteria (Figure 1). Tie et al report a correlation between changes in cfDNA mutation levels after one cycle of chemotherapy and response by RECIST criteria 8-12 weeks after the onset of therapy, and more importantly a trend toward a correlation between changes in ctDNA and progression free survival (PFS). Interestingly, although very early changes (d+3) in ctDNA did not correlate with response, a spike in ctDNA was observed in 3 patients with a striking response, suggesting that early changes in mutational loads in plasma may reflect DNA release into the bloodstream and may be a used to identify the best responders.

A test that anticipates response to a given drug early during the course of treatment without having to wait for image changes in the CT-scan weeks after the onset of therapy, potentially allows for an early switch in treatment, avoiding unnecessary side effects, enhancing efficacy and minimizing costs. Moreover, recent evidence shows

that early tumor shrinkage (ETS) in the treatment of metastatic colorectal cancer correlates with longer survival.

What are the implications of this work? The encouraging results in this paper support the use of ctDNA as an early indicator of tumor response in metastatic colorectal cancer patients. However, given the small size of the cohort, these data should be viewed as hypothesis-generating and must be replicated in the context of large clinical trials to show a clinically and statistically significant impact on survival of patients. From a methodological standpoint, the approach is relatively easy to translate in daily clinical practice. The approach requires availability of tumor-tissue (surgery or biopsy) to identify patient specific mutations. While this is rarely a limitation for colorectal cancer patients, in other tumor types such as lung tumors access to lesions is more difficult and may sometimes be a limitation.

The idea of assessing response to treatment in cancer patients using mutation levels is reminiscent of the use of viral load to monitor therapy response in HIV patients. Will ctDNA substitute RECIST in a near future? A number of reasons suggest that imaging will always be necessary to evaluate the site of metastatic disease, the resectability of tumoral lesions or the clinical compromise of adjacent anatomic structures. Therefore ctDNA and RECIST assessment will likely complement each other, and together with other methods (i.e., functional imaging) will define new integrated standards for evaluation of therapy in oncology. As highlighted by this study, the opportunities offered by circulating free tumour DNA are only starting to be explored but is already clear that liquid biopsies are here to stay and will become a central asset in the management of cancer patients.

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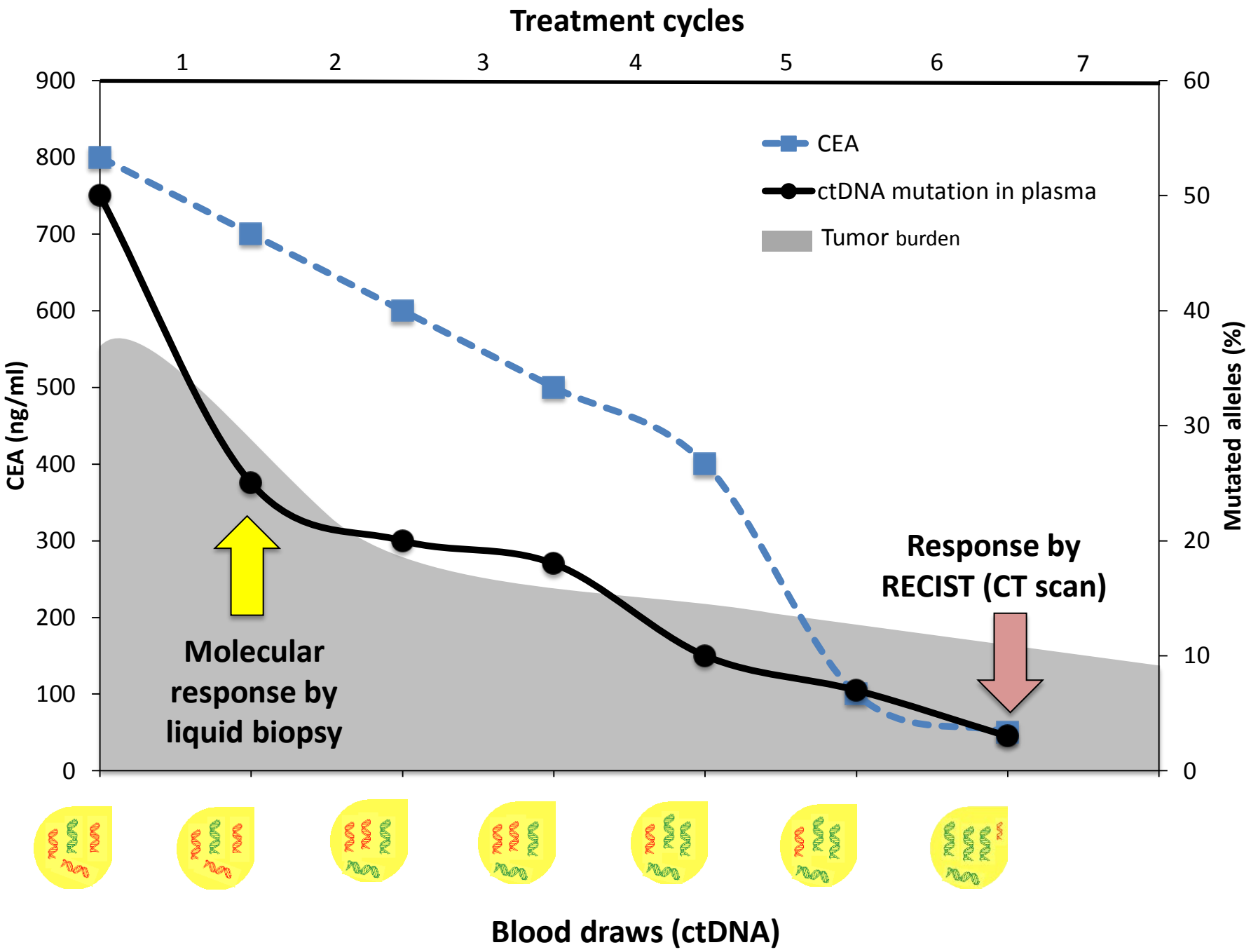
Treatment cycles
1
2
3
4
5
6
7
900
800
700
600
500
400
300
200
100
0
60
50
40
30
20
10
0
CEA (ng/ml)
Mutated alleles (%)
CEA
ctDNA mutation in plasma
Tumor burden
Molecular response by liquid biopsy
Response by RECIST (CT scan)
Blood draws (ctDNA)