The treating physician indicated that the blood sample was taken from the same femoral line through which cefotaxim had just been administered. Interference due to cefotaxim was confirmed by in vitro experiments (1, 2). It is advisable that blood samples should not be collected from lines used for drug administration.

A sample drawn from the antecubital vein had total protein of 7 g/dL.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

References

Circulating Tumor DNA: The Future of Personalized Medicine in Oncology?
Christopher B. Ryder¹,² and Christine L. Schmotzer¹,²*

Tissue biopsy has long served as the mainstream of cancer diagnosis, staging, and therapeutic decisions, with its role evolving from simple histologic examination to complex genetic analysis. Despite its utility, biopsy represents only a single time point from a single location, often proving inadequate at fully characterizing a malignancy and its evolution because nearby tissue might contain additional genetic information that would affect staging or treatment. Unfortunately, the invasive nature and inherent selection bias of biopsy limit its usefulness as a real-time monitoring tool. Newer technologies seeking to transcend this shortcoming include analysis of circulating tumor cells and their fragments, such as exosomes and DNA, in peripheral blood. A recent feature in Nature highlights advancements in the detection of circulating tumor DNA (ctDNA) for this purpose (1). This emerging methodology enables sequencing of DNA originating from lysed tumor cells present in a blood sample to follow tumor recurrence and to characterize genetic abnormalities that confer resistance.

Free DNA was first discovered in human circulation during the late 1940s, followed by isolation of tumor-specific genetic material in the 1970s. Yet, ctDNA methods for oncology have since lagged behind applications such as prenatal diagnostics. Challenges that have impeded its development and integration into clinical practice include highly variable, often low, ctDNA concentration in blood, especially in early stage tumors. Fortunately, technologic advancements in target selection and amplification methods as well as sequencing methodologies have facilitated the detection of these minute quantities. The authors describe one methodology, known as BEAMING (beads, emulsions, amplification, and magnets), which boasts an analytical sensitivity of up to 0.01% using enhanced and highly selective target capture. This exquisite detection capability has allowed researchers to explore the clinical applicability of ctDNA to cancer monitoring. A study published by Diehl et al. (2) showed early evidence of the strong negative predictive value of ctDNA, demonstrating that undetectable ctDNA levels following tumor resection correlate with the absence of tumor recurrence. Further work has confirmed this finding and demonstrated...
that ctDNA is measurable for a variety of advanced cancers.

Much like other serum cancer markers, ctDNA can detect residual tumor noninvasively. However, studies demonstrate superior diagnostic sensitivity of ctDNA over both protein biomarkers and circulating tumor cells for therapeutic monitoring. Moreover, by interrogating established resistance mechanisms, ctDNA may reveal impending expansion of low-abundance resistant clones earlier than current monitoring protocols. One example of this possibility is work showing the emergence of KRAS (kirsten rat sarcoma viral oncogene homolog) mutations in EGFR (epidermal growth factor receptor) inhibitor–treated patients on average 5 months before demonstration of tumor progression by surveillance imaging (3). However, this targeted approach is not universally applicable because it may overlook other equally relevant alterations. Researchers have detailed tumor heterogeneity and discovered unique paths to therapeutic resistance by the unbiased method of whole exome sequencing. Today, however, this approach is far too costly to be performed clinically. A proposed middle ground includes focusing on the portion of the genome most commonly mutated in specific cancers, an approach that, in theory, could minimize missed mutations while moderating costs.

Despite its impressive analytical sensitivity, ctDNA analysis currently remains insufficient at early detection of tumors. Some argue that further advances in technology will overcome this obstacle and make ctDNA a viable screening method. However, as with many ultrasensitive clinical methods, increased sensitivity carries with it new challenges in interpreting the clinical significance of the results. Do rare mutations in circulating DNA necessitate extensive workup for an occult malignancy? Do such abnormalities even possess malignant potential? Is ctDNA even truly representative of the tumor from which it comes? Despite the wealth of information this technology provides, the critical question remains as to how it can best direct clinical action to improve patient outcomes. Longitudinal studies are ongoing, pairing tissue biopsy with ctDNA “liquid biopsy” to address some of these questions.

As ctDNA technology pushes the boundaries of cancer detection, it has outdistanced the current armamentarium against cancer. A mutation driving resistance may be found, yet no therapy to target this aberrant pathway may exist. Still, although ctDNA may uncover as many undruggable as actionable mutations, its utility as a research tool is undeniable. And pharmacologic science may eventually catch up to our ability to understand cancer evolution by advanced genetic techniques like ctDNA analysis. As such, it may yet prove to be a critical component of realizing the ultimate goal of personalized medicine in oncology.

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References


Recommended Reading for Rookie LC-MS Users

Roy William Peake*

The love affair between laboratory medicine and LC-MS is showing little sign of waning. Clinical chemists have enthusiastically embraced LC-MS due to its often superior analytical performance and high-throughput capabilities. However, for clinical LC-MS users, the unique set of challenges with developing and implementing robust LC-MS methods...