Clinical Chemistry

Design of Tumor Biomarker-Monitoring Trials: A Proposal by the European Group on Tumor Markers

Article:
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Guest:
Dr. György Sölétormos is the Medical Director of the Department of Clinical Biochemistry, Hillerød Hospital, University of Copenhagen.

Bob Barrett: This is the podcast from *Clinical Chemistry*. I am Bob Barrett.

One of the major clinical applications for measuring tumor markers is in the monitoring of cancer patients over time. However, there is little in the way of published guidelines on just how to evaluate biomarkers for this purpose.

To address this, the European Group on Tumor Markers has convened an international multidisciplinary panel of scientists to develop guidance on the design of tumor monitoring trials. A report from this group appears in the January 2013 issue of *Clinical Chemistry*. The lead author of that report was Dr. György Sölétormos. He is the Medical Director of the Department of Clinical Biochemistry at the Hillerød Hospital, University of Copenhagen. He is our guest in this podcast.

Dr. Sölétormos, you and your group are addressing a subject of high interest for cancer patients all over the world as well as their treating physicians. Can you give us some background information on tumor biomarkers?

Dr. György Sölétormos: Yes, sure. First of all, I would like to thank both my colleagues in the European Group of Tumor Markers (EGTM), of which I am a member, and also the international panel of co-authors from Europe, the U.S., and Canada for their valuable contribution to this article. Without their continuous contribution and support the paper would not have reached so far.

Now getting back to your question about some background information on the tumor biomarkers. First of all, our article addresses tumor biomarkers that can

be measured in the blood, and these markers are denoted as serological tumor biomarkers.

The serological tumor biomarkers in routine use today, they are biological compounds released from tumor cells into the circulation and by taking a blood sample from a patient the concentration of a biomarker in the blood sample can be measured accurately in the laboratory.

However, most of the serological tumor biomarkers we use today are released not only from cancer cells, but also from the corresponding healthy tissue from which the cancer originates. Therefore, the tumor biomarkers are also present in the circulation among healthy individuals without cancer.

Bob Barrett: Why are tumor biomarkers used for monitoring of malignant disease?

Dr. György Sölétormos: Well, generally speaking the concentration in the blood stream of the biomarkers in routine use today depends on the number of biomarker-producing cells. When a tumor arises, grows and eventually develops metastases, the number of biomarker-producing cells will increase.

Therefore, the concentration of a biomarker will be higher in the blood sample from cancer patients as compared to healthy individuals and patients with benign disease.

The cancer biomarkers in routine use today are indicators of a tumor burden. When the number of cancer cells increase during tumor progression the concentration of the marker will increase, and when the number of marker producing cells decrease during tumor shrinkage the concentration of the marker will also decrease.

Bob Barrett: And how do patients benefit from such tumor biomarker monitoring?

Dr. György Sölétormos: Well, that is a very relevant question of course. Cancer biomarkers can detect smaller tumor burden or a smaller change in tumor burden than imaging techniques. Cancer patients can benefit from being monitored with several biomarker determinations because biomarkers can provide earlier information on changing tumor burden than imaging techniques, the example is CT scans and MR scans.

Thus, decrease of tumor biomarker concentrations after intentional chemotherapy can provide early information

on tumor shrinkage, and inform the patient and the doctor that the therapy is working and should be continued in spite of adverse effect.

On the other hand, increase in tumor biomarker concentrations can provide early information on tumor growth and thus be valuable when deciding whether to stop the current therapy and initiate a new therapy.

Bob Barrett: Now over the past 10 to 20 years research looking into tumor biomarkers has intensified but the utility of monitoring tumor markers is still being debated. How does your report help clarify their role?

Dr. György Sölétormos: Well, first of all the paper is based on the consensus from an international panel of scientists representing oncology, laboratory medicine, epidemiology, and the diagnostic industry actually. Taken together, the group of authors has many years of experience and several hundreds of publications within the field of biochemical diagnostics with special focus on tumor biomarkers.

We have used the broad spectrum of competences represented within the authors' group to develop a set of guidelines on how to design, develop, and conduct monitoring studies based on tumor biomarkers, and of course it's our hope that by providing these guidelines systematic well-designed evaluation of biomarkers from monitoring may enable that earlier use in evaluating response to cancer therapy with a stronger evidence base.

Bob Barrett: So doctor, what is particularly new in this *Clinical Chemistry* report?

Dr. György Sölétormos: Well, our article outlines a new design format for monitoring studies involving tumor biomarkers. We have been inspired by the four-phased approach as used routinely in clinical drug trials, for example, in oncology, because this format should be easy to comprehend, both for doctors in oncology as well as laboratory medicine.

Bob Barrett: Clinical trials usually have different phases. Could you help explain the design of these different phases of trials for tumor marker of monitoring?

Dr. György Sölétormos: Yes. Phase one monitoring trials, explore the correlation between a change in tumor burden and a change in several biomarker concentrations, and the strengths of correlation between changing tumor burden and marker concentration will influence it with utility of the marker to reflect disease activity.

Phase two monitoring trials, estimate the ability of several biomarker measurements to identify, exclude, and predict a change in tumor burden. And of course to be useful for monitoring a cancer biomarker should provide early and reliable signals of changing tumor burden.

Continuing to phase three monitoring trials, they compare whether or not early biomarker guided intervention results in improved patient outcome and the phase three trials are based on randomization.

In phase four monitoring trials, they evaluate the long-term overall survival and the adverse effect following early tumor biomarker intervention in routine use.

Phase four trials also address cost benefit. Meaning whether investment in marker monitoring programs improve quality of life and they provide cost savings in the long-term. Additionally, phase four trials should also address cost effectiveness whether increased costs associated with incorporation of the biomarker into routine monitoring improve patient outcome.

Bob Barrett: Does the phased design format applied generally to tumor biomarkers?

Dr. György Sölétormos: Absolutely. Major efforts are focused to identify biochemical compounds that may be used to monitor the activity of disease among cancer patients. After identification and biochemical characterization the compound should follow a standardized four-phased evaluation as proposed in our paper on design of tumor marker monitoring process.

Bob Barrett: Well, doctor, let's look ahead. Where do you see cancer biomarker research going in the coming years?

Dr. György Sölétormos: In my opinion the search for new and possibly more specific tumor biomarkers will continue with increased pace.

We will see new protein markers as well as evaluation of methylated DNA fragments and MicroRNA in serum, and additionally most interesting, future research will also focus on the clinical utility of identifying circulating tumor cells in the blood.

Bob Barrett: Well, doctor, finally do you some final words for our listeners and of course the readers of *Clinical Chemistry*?

Dr. György Sölétormos: Yes. First of all, thank you for this opportunity to expand on our article *Design of Tumor Biomarker: Monitoring*

Trial. We are encouraged to later present guidelines to serve as inspiration when monitoring markers are evaluated for their clinical utility. Establishing the clinical utility of a biomarker for use in monitoring requires careful trial design such as those described in our article.

Standardization of the evaluation process may facilitate a faster implementation of a reliable monitoring marker into routine practice for the benefit of the patients. However, if monitoring markers are to be clinically useful for prediction, effective treatment options that can benefit from early information provided by several marker measurements must of course be available.

Bob Barrett: Dr. György Sölétormos is the Medical Director of the Department of Clinical Biochemistry, Hillerød Hospital, University of Copenhagen. He has been our guest in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening!