ASCO President George Sledge Discusses the Challenge and Promise of the Genomic Era

By Susan Beck

In his plenary address as outgoing president of ASCO, Dr. George Sledge proposed that we are on the brink of a new era in cancer therapy—an era of genome-based treatment. He stressed that this new “genomic era” holds great promise for patients, citing as evidence a recent paper in JAMA that described a case in which the results of deep sequencing of a patient’s leukemic cells led to successful individualized therapy.

Cancer treatment to-date, he said, can be roughly divided into three eras: the era of local-regional therapy, which began in the early 1900s; the era of nonspecific systemic therapy, which started in the late 1940s; and the era of targeted therapies, which has come into its own in the last decade—and which is still very much with us.

Dr. Sledge’s proposition that oncology is entering a new era is predicated on the great strides that have been made in recent years in the sequencing of both tumor genomes and host genomes. Today, the genomes of several thousand cancers, covering 20 major tumor types, are being sequenced. And the advances that are being made in the sequencing of individual patients’ genomes have caused the price of whole-genome sequencing to fall so rapidly that the age of the “$1000 genome” is in sight. That is the cost point at which personalized genomic medicine becomes possible.

The chief reason the genomic era presents such a challenge is the discovery—resulting from work in tumor sequencing—that a large number of cancers are what Dr. Sledge described as “smart cancers” (as opposed to “stupid cancers”). “Stupid cancers,” which have been a large focus of research in the era of targeted therapy, are those with a low mutational load and a single “driver” mutation. The discovery of a drug that targets that driver mutation is a reliable formula for success in stupid cancers, a good example being chronic myelogenous leukemia, in which the use of imatinib to target its driver BCR-ABL translocation results in a high response rate and long survival.

“Smart cancers,” on the other hand, have a high mutational load (from 10 to as many as 100 mutations per megabase) and multiple drivers. Unfortunately, many common cancers are smart cancers. Among the best known examples are non–small-cell lung cancer (NSCLC) and melanoma. One reason NSCLC has been resistant to so many different drugs is that these tumors—especially those in patients who are smokers—have such a high mutational load. Another “smart” feature of
cancers that is being revealed by genomic studies is the ability to evolve: primary tumors can give rise to metastases and secondary metastases that are genetically different from the tumor from which they derive.

What all this means for oncologists is that to deal with the mutational chaos represented by smart cancers and evolving tumors is essentially to deal with a host of orphan diseases. “There will be no ‘magic bullet’ for these tumors,” Dr. Sledge said, since they don’t have a single driving mutation. Instead, he proposed that “we need to think in terms of a ‘magic shotgun,’ loaded with pellets aimed at multiple targets in multiple pathways.”

Of course, another way to tackle the problem is to approach it from an entirely different angle. Dr. Sledge suggested that approaches other than attacking multiple targets simultaneously might become more attractive in the new genomic era. Such approaches include increasing efforts at cancer prevention, harnessing the power of the immune system, focusing on interfering with DNA damage repair mechanisms, altering the tumor microenvironment, utilizing metastasis suppressor gene products, and attacking cancer stem cells.

However, the need to test multi-target therapies in clinical trials cannot be evaded. Such trials will play a key role if we are ever to achieve cures for the more complex tumors—and designing them is a daunting challenge. Dr. Sledge demonstrated that the number of patients who would need to be screened to enroll a single patient (a concept he termed the “number needed to study”) in a trial involving two targets and a two-drug combination would be 154. That number would rise rapidly were even more targets to be involved.

To be able to meet this challenge of attacking multiple targets at once, our clinical trials system will not only need new trial designs (a departure from the single-drug study that has been more or less the standard until now). It will also require extensive health information technology systems that can link clinical researchers, drug developers, tissue banks, and laboratory scientists around the world; that can offer support to patients and physicians who must make the increasingly complex treatment decisions associated with genomic medicine; and that can aggregate data so that researchers can learn from every patient’s experience. Also needed, Dr. Sledge noted, will be better guidelines—easily accessed, more user-friendly, and flexible enough to address the scores of new “orphan diseases” that genomics will reveal—along with improved measures of performance.

Dr. Sledge closed by reminding his colleagues that for all the change that the new genomic era will require, one thing will remain constant: the skill, care, and compassion for their fellow human beings that oncologists have always brought to their work with patients.

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