Best Targeted Sarcoma Treatment: Advances from the Musculoskeletal Tumor Society Annual Meeting

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Targeted, personalized therapy is the mantra in contemporary oncology. So how does orthopaedic oncology fit into the new paradigm? In the rapidly changing political, legal, and medical landscape, there are challenges and successes for musculoskeletal cancer patients, practitioners, and researchers as we try to implement individualized therapies. The Musculoskeletal Tumor Society (MSTS) leads, captures, and reflects the societal dynamism that will determine how personalized medicine applies to bone and soft tissue tumors through the activities of the MSTS members (Fig. 1), their annual meeting, and the selected papers published in this *Clinical Orthopaedics and Related Research*® symposium.

During this past year, three major regulatory and legal changes have occurred: (1) the U.S. Supreme Court ruled [1] that genes cannot be patented, (2) the FDA approved [6] genome-wide genetic testing, and (3) the FDA restricted [7] the company 23andMe Inc.

The landmark Supreme Court decision overturned the patent granted for the BRCA test that gave Myriad

Genetics Inc. a monopoly on the breast cancer gene test. The Supreme Court decision unburdened the developers of commercial genetic tests from worrying about having to pay a royalty fee for every gene included in a genome-wide screening.

The recent FDA approval of genome-wide genetic testing jumpstarted personalized medicine. This new technology uses the MiSeqDx Instrument (Illumina Inc, San Diego, CA, USA), which is the result of decades of NIH genetic work [2]. The price has plummeted to approximately USD 5000 for whole genome sequencing performed in less than 24 hours. Because of this, large numbers of people will be able to afford, and will likely yield, real-time data for patient-physician decision making. This sets the stage for financial approval of the testing to meet what will undoubtedly be high demand from a public whose appetite for this information has been whetted by an overly-optimistic press coverage of the widespread potential of this methodology to cure cancer. The interest and belief in the method is not an unmitigated good. We will soon be inundated with comprehensive genetic information and not have the technology or clinical ability to integrate this data into current clinical practice. Among the challenges will be to identify the correct targets, and figure out how to deal with the unexpected identification of disease susceptibility, predictive, or modifying genes. This genetic information has already been found important, modifying the metabolism of and response to at least 120 drugs, so called “genetic pharmacology” [6].

In late November 2013, the FDA directed the discontinuation of the sale of the saliva-based DNA test that the company 23andMe Inc. contends can identify genes for 242 diseases for a mere USD 99 [7]. The ethics, privacy issues, and scientific validity of this type of testing, especially when directly marketed to the public requires careful

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consideration and continued input from oncologists. Appropriate use of the sophisticated genetic testing will remain at the top of the agenda of the public, government, and the medical community. Targeted therapy requires accurate and precise genetic information correlated with accurate clinical outcome data. The members of the MSTS have an obligation to contribute to the discourse in many ways, including procuring the highest quality tissue samples with fidelity, and accurate reporting of outcome data.

Genetically based, personalized therapy is the Holy Grail of modern oncology. Its pursuit may be quixotic when we are faced with a patient who is in need of immediate care due to a sarcoma, and all theory will be pushed aside. Surgery is the practical answer. Anatomically based therapy remains the cornerstone of orthopaedic cancer care in 2014. Aided by more sophisticated imaging and intraoperative navigation, more joints and growth plates can be saved. Greater surgical skill is able to preserve more uninvolved normal tissue by narrowing safe margins. The combination of accurate imaging and accurate surgery is the true modern definition of “targeted therapy.” Until genetic targets are refined and therapies identified, careful orthopaedic surgery is our best strategy and supersedes all other approaches. While we need better data, and even “big data” to make a difference [3], surgery has an important role to play. Good surgery remains the “cancer weapon we need most.”

A simple comparison of response rates would tell the story. Most chemotherapy drugs achieve only a 2% complete response and 25% partial response against most cancers. Targeted therapies such as Sutent[®] (Pfizer Inc, New York, NY, USA) are transformative for the treatment of renal clear cell carcinoma, yet they only achieve up to a

30% response rate [4]. More focused treatments such as Gleevec[®] (Novartis Pharmaceuticals Corp, East Hanover, NJ, USA) for gastrointestinal stromal tumors have a modest response rate that, unfortunately, is not durable. Resistance develops in time, showing how redundant biologic pathways frustrate targeted therapies [5]. Attacking the tumor with several agents working from different directions holds promise to circumvent the therapeutic resistance. Medical oncology is only to the point of taking a “basket approach to attack the “driver” mutations present in many seemingly disparate cancers [1]. Surgery is more targeted and effective. Surgical resection routinely gets a 100% complete response when we obtain a wide surgical margin. It is also generally durable, with only a single-digit percentage rate of local recurrence, and a moderate metastatic rate compared to the native reported rates.

The papers presented at the MSTS meeting continue to lead the way in this effort, narrowing surgical margins, striving to keep local recurrence rates low, and increasing the durability of reconstructions while defining the genetic correlates of musculoskeletal tumors. Orthopaedic oncology is essential to translate the genetic results and make targeted therapy a reality. The MSTS continues to play a leading role in this dissemination of knowledge and translating this as a viable option.

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