The Median Isn't the Message

In his letter last month, Dr Daniel George discussed the term "outcomes" in oncology research and how it applies to patients. One impression I was left with after reading his editorial is how unproductive it can be for cancer patients to hear only median values. Although half of patients fall on each side of the median, the majority of patients can be located away from this value unless the curve makes a perfect bell shape. We see this in hematology when a patient with microcytic anemia has two distinct populations of red blood cells after receiving a blood transfusion. The mean corpuscular volume may be normal, but none of the individual cells match the mean. Use of the mean can hide important information regarding red blood cells; does using the median do the same regarding subgroups of patients?

Two quotes regarding statistics come to mind. The first quote, by William Winwood Reade, is cited by Arthur Conan Doyle in his book, *The Sign of Four*. In it, Sherlock Holmes remarks to Watson, "While the individual man is an insoluble puzzle, in the aggregate he becomes a mathematical certainty. You can, for example, never foretell what any one man will do, but you can say with precision what an average number will be up to. Individuals vary, but percentages remain constant." This quote exemplifies the idea that statistics are useful for predicting how a population will do, but not an individual. The second quote, by Stephen Jay Gould, is that "the median isn't the message." In his essay by the same title, he described his odyssey with mesothelioma. Told of the 8-month median survival for his condition, Gould set out dissecting the statistics to glean any signs of hope. As it turned out, Gould survived another 20 years, dying of a different cancer. He was part of the right-skewed curve that provides hope to all of our patients with terminal cancer.

In my research for this editorial, I did a web search for "the median isn't the message." Although I expected most of the top hits to be websites dealing with statistics, most turned out to be patient information pages on how to handle a cancer diagnosis. As an oncologist, it is obvious to me why this message, and the hope of being part of the right skew, is so important to patients. They need this hope, and uncertainty regarding the timing of their death, to be able to start each day. Nobody can predict the future nor how long someone is going to live, yet we discuss, in a definitive fashion, the available data with our patients and provide them with a time frame. I always educate my new patients by telling the story of a patient who came to our clinic 6½ years after being diagnosed with CLL and being told of a 7- to 9-year life expectancy. This still-untreated CLL patient was devastated by the thought that his life expectancy was just another ½ to 2½ years. To date, this patient remains untreated.

The second aspect of this discussion relates to the identification of subsets of tumors. We have seen the number of distinct lymphomas increase from 15 in the 1982 National Cancer Institute Working Formulation to more than 90 in the 2017 World Health Organization classification. Molecular biology has enabled us to separate out subgroups with the hope of generating more-uniform clinical entities. Prior to the Revised European-American Lymphoma Classification, many cases of mantle cell lymphoma were classified as CLL. These patients misdiagnosed with CLL did worse than the overall CLL group. Separating out the mantle cell patients therefore resulted in two more-homogeneous groups. By looking at the extremes of our patient curves, we may be able to discern clinical differences that reflect differences in cell biology. This phenomenon will probably become more relevant with the increased use of targeted therapies.

In her interview in this issue on immunotherapy for breast cancer, Dr Leisha Emens describes the data for nab-paclitaxel plus either atezolizumab or placebo in untreated women with metastatic triple-negative breast cancer. Although the median overall survival was not significantly different between those treated with immunotherapy and those treated with placebo, the data look very different when PD-L1 expression is factored into the analysis. Among patients with PD-L1–expressing tumors, atezolizumab was able to prolong median overall survival from 15.5 months to 25.0 months, leading to FDA approval of the combination in this subgroup.

Such an outcome underscores the importance of identifying subgroups that are most likely to benefit from a proposed treatment, and designing clinical trials to reflect this. The problem is that clinical trials become increasingly difficult and expensive to perform as subgroups become smaller. We must work with the FDA to ensure that the subgroup approach does not impede our ability to develop new treatments.

Sincerely,

Richard R. Furman, MD