The Return of the Emperor

A common topic of discussion in my clinics over the past week was patient impressions of Ken Burns' film adaptation of Siddhartha Mukherjee's *The Emperor of All Maladies*, a biography of cancer.

I had read the book several years ago, was suitably impressed, and used it for our first book club. Now patients were viewing the film version, with mixed emotions. Some were frightened by part 1, with its graphic descriptions of excessive surgeries and harsh chemotherapies. Other felt uplifted by the signs of progress. The book and the PBS special were rather different, but quite complementary. Both were epic in scope and volume, with just a few liberties taken with the truth.

The book was a historical account of the most pervasive of diseases, whereas the film added more patient stories. Some patients had favorable outcomes, such as the breast cancer surgeon who had developed bilateral breast cancer. Others dealt with the disappointment of treatment failures. The film also related how the development of targeted agents, including trastuzumab (Herceptin, Genentech) for human epidermal growth factor receptor 2–positive breast cancer and imatinib (Gleevec, Novartis) for chronic myeloid leukemia, changed the world of cancer treatment and gave hope for similar agents in other diseases—although I must say that the lack of mention of rituximab (Rituxan, Genentech/Biogen Idec), the monoclonal antibody that revolutionized lymphoma therapy, was an egregious omission.

The lessons learned from this video portrayal of cancer were many. Unfortunately, too many lessons were learned the hard way. When I was at the National Cancer Institute, a favorite slide from my lecture on new agents was the one that read, "More isn't better: different is better." Last night I heard that phrase echoed several times during the parade of the Emperor.

For example, the film explained the history of the disfiguring Halsted radical mastectomy (my mother and her identical twin sister both underwent this procedure for their stage 2 disease, and suffered for many years from the resulting lymphedema), and the major improvements in quality of life for thousands of subsequent women rescued by the National Surgical Adjuvant Breast and Bowel Project studies conducted by Bernard "Bernie" Fisher, who was appropriately deified. It also described the widespread use of high-dose chemotherapy requiring autologous stem cell rescue in breast cancer outside of clinical trials. The zealots who promoted this approach virtually impaled clinical research for years. As we all know, clinical trials later revealed a clear lack of benefit despite the cost and toxicity of the procedure. The line was a bit blurred between the villains and heroes, each of whom claimed it was all in the name of progress!

But the clear and resounding message that Burns and Mukherjee left with us was one of hope; hope that through a better understanding of the biology and genetics of the Emperor we can move treatments from the draconian to the targeted. Instead of infusing derivatives of nonspecific, noxious substances such as mustard gas (the ubiquitous alkylating agents), we can now harness the immune system to do the fighting for us.

This theme was reiterated in a second television show that stimulated almost as much interest among my patients: the recent episode on *60 Minutes* in which researchers at Duke University used an attenuated polio virus to treat glioblastoma in a phase 1 trial. The first 2 patients were in prolonged remission, although about half of the patients in the phase 1 study died. Although many in the oncology community criticized the piece as irresponsible journalism based on premature data, I was cautiously enthusiastic about what I saw, just as I am cautiously enthusiastic about the early results with chimeric antigen receptor T-cell therapy. However, as I wrote in my February 2012 Letter From the Editor, "Clinical research should be conducted by enthusiasts, but reviewed by skeptics." It remains to be seen whether these exciting possibilities will ever play in Peoria, or fade in the glow of newer agents that inhibit programmed death 1 and its ligand, B-cell receptor signaling pathways, BCL2, or other features that make the cell malignant.

What I am certain of is that we are in a new age, one unanticipated by the warriors of yesteryear, such as Sidney Farber, Mary Lasker, Emil "Tom" Frei, and others. All it will take will to get the job finally done will be to get a good peek at what is really under the Emperor's new clothes.

Until next month . . .

Bruce D. Cheson, MD