LETTER FROM THE EDITOR

Cheson's rule of drug development: The efficacy of a new treatment directly correlates with its negative impact on clinical research.

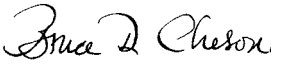
I was asked to give a talk at the European School of Oncology in mid-June, the afternoon prior to the start of the International Conference on Malignant Lymphoma (ICML). The venue was on Monte Verità above the idyllic little town of Ascona, Switzerland, just a bit more than an hour from the ICML meeting in Lugano. Ascona, which sits on Lago Maggiore, was notorious for once housing an artist colony and a counterculture retreat for those who preached a return to nature (read—nudist colony). For a variety of reasons, the retreat lost its literal shirt and was taken over; the facilities are now a conference center. The topic I had been assigned to discuss was "Challenges in the design and interpretation of early clinical trials in haematologic malignancies." The subject was a challenge unto itself. I asked the chairmen of the meeting on what exactly they wanted me to reflect, and was told they wanted me to show how best to avoid getting overly excited about drugs that eventually didn't pan out (false positives), while limiting the false negatives. I knew that I would have to make the talk original, creative, educational, and, most importantly, entertaining.

There were about 80 attendees at the conference, mostly at the fellow and junior faculty level, who arrived from numerous countries around the globe. I started off with a brief history of clinical trials, dating back to the Bible, and described the various phases of studies. I talked about the Will Rogers effect and how it has come into play as a result of more sensitive diagnostic tools, such as CT-PET, and about the effect of stage shift on historical comparisons. The flood of new, targeted agents requires the recognition that attacking a single receptor or pathway is as likely to eradicate most tumors as a matador with a rubber lance is of felling a charging bull. I reinforced that the goal of individualized therapy could be realized only with a better understanding of tumor biology and genetics. I suggested to the eager students that to temper premature enthusiasm for drugs, we should require multiple smaller studies, focusing less on the waterfall plot than on clear evidence of clinical benefit. Limiting the improper flushing of a novel agent (which I referred to as *pharmacoptosis*) would be best served by a study in a population enriched for the appropriate target.

But, once we identify a drug with promise, how do we get it to market? Drug development has become increasingly challenging. For most hematologic tumors (CML being a notable exception), we lack validated surrogate endpoints. Thus, a great deal of imagination is required because of what I, by default, have named "Cheson's rule" (vide supra). A number of years ago, I gave a talk with the subtitle "How rituximab has destroyed clinical research in lymphomas." Now, don't get me wrong, I think "Vitamin R" is one of the most—if not the most—important advances in the treatment of B-cell malignancies. I could give a similar talk substituting "bendamustine" and, perhaps, in the near future, the extremely promising brentuximab vedotin. Here's how it goes—a new drug enters clinical trials and dazzles us with its activity, so much so that it is rapidly moved up as part of frontline therapy. The result is that there are no longer drug-naïve patients against which to compare a newer drug in the relapse setting. The remarkable efficacy of R- or B-based upfront therapy, or even ABVD in Hodgkin's, requires that a new drug be a real winner to be effective in patients resistant to these active regimens; however, the number of these agents that are left is dwindling, and focusing on them is a risk few companies are willing to take (here brentuximab was a splendid exception, but now upfront it goes). So, either the companies have to identify a clinical subset of patients to call their own, and for which the FDA is willing to accept single drug–single arm data, which is tricky, or they are stuck with a design such as R (or B or ABVD) +/- the new drug, with approval by regulatory agencies forever linking them with the other agent(s). 'Tis a puzzle. Thus, the more effective a therapy, the more difficult it is to find a niche where subsequent agents can show their stuff. As our treatments get better and better, the harder it will be to get drugs approved for those patients who are the most problematic.

Now, recent events suggest that I will have to come up with a corollary for my rule for some other drugs that make their way to the market on hope and promise, but which seem to fizzle the more we learn about their limited efficacy and substantial toxicity in certain indications (eg, the recent turmoil over bevacizumab in metastatic breast cancer). For now, I will safely remain on my own hematologic turf.

Until next month . . .



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