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LETTERS

George A. Omura, MD, on Giving, and Not Giving, Chemotherapy

Since my name was mentioned in the correspondence between Drs. Joseph Simone and Elizabeth Lowenthal in the Letters section in the June 25th issue regarding Dr. Simone's "Econo-Docs" column, I would like to comment briefly about what I said and wrote more than two decades ago.[1]

I thought a goal should be set for each patient, based on what was realistic, not wishful thinking. Is cure a realistic possibility? Has a survival benefit been proven in other patients with that stage and type of cancer? Is relief of symptoms likely? Does the patient consent to a study?

Finally, the need for psychological support (something is being done; someone cares) as an indication for giving chemotherapy, although disparaged by some of my colleagues, seemed to have some legitimacy. The patient who insists on chemotherapy (as opposed to the family or referring physician) and is not ready for hospice care is well known to practitioners like Dr. Lowenthal. However, the point was also made that, at least in my experience, there were cases where none of these indications pertained, and thus there was no reason to give chemotherapy.

Too naïve, perhaps? Nowadays, are medical oncology trainees taught to set a goal for each patient and to establish a legitimate reason for giving chemotherapy? The cancer chemotherapist gives chemotherapy; the medical oncologist should know when not to give it.[2]

George A. Omura, MD
Professor Emeritus
University of Alabama at Birmingham

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1. Omura GA: Indications for cancer chemotherapy. New Engl J Med 1982;307:826.
2. Omura GA: Oncology (the study of cancer) is more than chemotherapy. J Clin Oncol 1993;11:1837.

Reply from Joseph Simone, MD

Thank you, Dr. Omura. Your words of wisdom remain true today, and perhaps even more salient. It takes a conviction to do the right thing and a willingness to help others see it. This is often difficult in high-pressure practices like oncology, but it is our responsibility to provide such guidance.

Viewpoints

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Stopping Rules

In my opinion, when possible, clinical trial designs should be "adaptive." In particular, in Phase II and III trials, physicians should examine the response rate in patients already treated with a new agent, and if this rate is unacceptably low, the trial should be stopped so that future patients can receive different therapy.

"Stopping rules" depend on the "response rate of interest," also called the "target response rate." It is intuitive that the higher the target response rate, the fewer patients who fail to respond are needed to stop a trial. In at least several instances, the target response rate specified in Phase II industry-sponsored protocols is lower than the response rate with standard therapy.

Let's say the standard complete response (CR) rate is 50% and the target CR rate with the new drug is 20%. That means that only five patients must fail to respond to effectively rule out a 50% CR rate, whereas 14 would have to be treated to similarly rule out a 20% CR rate.

Thus, nine additional patients would have to be treated with a new drug after it is obvious that the new drug is less effective than the standard drug with respect to the outcome being monitored.

Informed consent forms routinely do not mention this practice, which is done in the hope that the new drug will produce responses less than complete—i.e., minor responses—in the additional patients.

> *"The pharmaceutical industry has been, and remains, indispensable if medicine is to move forward. It is a mistake, however, to ignore the industry's imperfections."*

There may be benefits to patients even if the CR rate is lower; for example, minor responses might prolong survival, or toxicity might be less than with standard therapy.

However, stopping rules are almost invariably designed so as to monitor only one outcome, generally response rate. Endpoints such as survival or toxicity are frequently monitored on an ad hoc basis.

Such informality is antithetical to accepted statistical practice and invites subjectivity into decisions about stopping/continuing clinical trials.

It is particularly unfortunate that this practice occurs given the availability of statistical designs that monitor multiple endpoints, e.g., response, toxicity, and survival.

For example, I know of one ongoing trial with no plan for stopping based on CR rate, even though the CR rate with standard therapy is 60%. The pharmaceutical company rationalized this omission by noting that the protocol involved treatment with two standard drugs in addition to the one investigational agent; this type of reasoning ignores the possibility that the investigational agent could make the standard drugs less effective.

It would appear that these practices leave pharmaceutical companies vulnerable to suggestions that they are more interested in furthering the interests of the drug (by observing some minor responses that may be of no benefit to the patient) than in furthering the interests of the patient.

Unnecessary Testing

The last point is that pharmaceutical-sponsored trials have occasionally made certain tests mandatory instead of optional, as they had invariably been in the past. To be included in the trial, patients have to agree to tests whose results, although of undoubted scientific interest and potentially beneficial to future patients, are irrelevant to the patient participating in the trial. Such tests include extra blood draws and bone marrow aspirations.

Regardless of the pain involved (and marrow aspirates are painful), the concern is that patients are being placed in an untenable situation that some might consider coercive.

I would suggest making the tests optional so that study participants can refuse the tests but still be able to be treated with the new drug. It is unethical to deny patients treatment if they refuse unnecessary testing.

I reiterate that the pharmaceutical industry has been, and remains, indispensable if medicine is to move forward. It is a mistake, however, to ignore the industry's imperfections.

The fundamental principle of medicine is to give the best treatment to each patient regardless of other considerations. I fear that this principle is being ignored in many industry-sponsored trials.