The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Between Scylla and Charybdis — Oncologic Decision Making in the Time of Covid-19

Mark A. Lewis, M.D.

"Doctor, should we activate the sepsis protocol?" my medical assistant asked with obvious concern. I triaged the patient in question. The metrics that had caused alarm at intake were tachycardia and tachypnea, but there was no fever or hypotension in this middle-aged woman. On exam, she was indeed breathing quickly and had a rapid, regular pulse, but there were clues beyond the vital signs as to the cause of her distress. Her eyes were as wide as her dilated pupils. Her skin was diaphoretic, and her feet tapped percussively on the tile floor. After some questioning, all evidence pointed to a hyperadrenergic response to extreme anxiety.

I am a medical oncologist. With distressing frequency, I tell people they have cancer, adding a brutal coda for many that their condition is incurable. A consultation with me is often accompanied by the tinnitus of terror — the patient hears the declarative confirmation of malignancy and then nothing else. In my professional capacity, I am used to witnessing primal fear, but I have never seen such widespread panic in my patient population as during the advent of SARS-CoV-2.

As an oncologist, I am also accustomed to framing danger in terms of proportions. In the calculus of difficult judgments, I try to demonstrate to my patients that the well-known side effects of chemotherapy are worth hazarding, presenting a risk–benefit ratio that I hope will not seem unacceptably top-heavy. When administering cytotoxic drugs, I carry in my head a repository of percentages — a 37% chance of neutropenia with a certain combination regimen versus only a 13% chance when a single agent is deployed, for instance — whereas my patients are understandably less empirical. Their choices often stem from their amygdala, their fear center, more than any other part of their brain. And so theirs becomes a relative assessment of threats to their person. In the ledger of horrors, for them to proceed with myelosuppressive treatment, their natural revulsion to "poison" must be superseded by their dread of an unopposed cancer.

Every patient's balance sheet looks different. For some, no chance of therapeutic benefit is too slim to lose its seductiveness, still enticing even when hope for a positive outcome looks razor-thin. In my career I have been astonished at how many patients have been willing to accept nearly

inevitable toxicity for the vanishingly small possibility that they will be one of a select few "exceptional responders."

At least, that is, until now. While the worldwide health community grapples with the novel contagion, the starkest end point in the outbreak has been the rising tally of lives claimed by Covid-19. As the deaths have mounted, it has also been common for the case fatality rate to be reported to the public; I have seen many patients under my care struggle to process that grim fraction in the context of all the other statistics I already cite to them. Chemotherapy, hardly desirable at the best of times, may never have been less appealing.

Although this pandemic poses danger in the most global sense, certain subgroups appear particularly vulnerable to critical illness and death. Chinese investigators reported that patients with cancer affected by Covid-19 had a risk of the composite end point of invasive ventilation, admission to the intensive care unit, or death as high as five times that among patients without cancer.[1] Even a remote history of cancer seemed to multiply the risk of severe events, possibly owing to protracted immunodeficiency,[2] although that association may be correlative at best, and the increased risk might be more closely tied to older age.[3] Confounding factors notwithstanding, most people with cancer, in comparing themselves with their healthy peers, perceive themselves as at greater risk from Covid-19, especially if they are actively undergoing therapy.

"Are we still friends?" is the half-joking question I have long asked any patient to whom I've administered chemotherapy for the first time. The initial treatment is instructive and clarifying for both of us. In the era of shared decision making, we commence treatment only after the hazy prophesying required for obtaining informed consent, in which I deliver a litany of potential outcomes before advising patients that, all things considered and in my professional medical opinion, they ought to sign on the dotted line. For all the gathering darkness, the future looks bright.

How different things can seem at our next encounter, ideally during a scheduled office visit but sometimes in the emergency department, on the hospital ward, or in the ICU. That laundry list of possibilities with which I deluged them at our previous appointment has now been narrowed, distilled into a present reality that might include intractable nausea, cholera-like diarrhea, or febrile neutropenia. Clouds have intruded on a sunny forecast, and it's time for the meteorologist to accept blame.

Infection is not a new worry for the medical oncologist to consider in this dangerous balancing act between competing threats. One of my most indelibly tragic memories from fellowship was the admission of a young mother during her first cycle of dose-dense chemotherapy for breast cancer. Although she could not have looked more robust embarking on treatment, and despite prophylactic myeloid growth-factor support, her white cells plummeted to near-agranulocytosis and she became truly septic. She was admitted in multiorgan system failure and rapidly died while on vasopressors and a ventilator. Despite every best effort, I could not, in the end, rescue her at her nadir. It still haunts me.

Each time I prescribe chemotherapy, the ethics lessons from my first year of medical school resound accusingly in my head: *primum non nocere*. To a student, it seemed a self-evident, easy morality (and didn't I sound sophisticated saying it in Latin?). But it turns out to be a precept that's extremely hard, if not impossible, for a medical oncologist to follow. I am a blunt instrument, and I cause collateral damage even when I take careful aim at an often elusive target inside a human being.

People, including physicians, do not often stop to think how, exactly, cancer kills. They are aware of its often mortal ultimatum without considering the means to its ends. It is rare, for instance, that the primary tumor grows so large that its size alone proves fatal, although such a direct outcome is certainly possible in cases of, for example, a colon cancer obstructing the bowel. More often, the cause of death is the downstream derangement of physiology, or the exquisite vulnerabilities of immunosuppression, whether intrinsic or iatrogenic.

My queasy conscience now wrestles with the possibility of a bimodal peak of cancer patients dying: the imminent spike of those with decimated immunity falling victim to Covid-19 and the latent toll on those whose treatments were de-intensified, delayed, or canceled altogether. To survive SARS-CoV-2 only to then succumb to an undertreated cancer would be a Pyrrhic victory. The acuteness of infection and the chronicity of malignancy are the Scylla and Charybdis between which oncologists and their patients must now chart a very cautious course indeed.

When I ask a patient who is

undergoing chemotherapy whether we remain friends, it is a feint toward an admission of guilt. I recognize that our therapeutic alliance mirrors an abusive relationship: I inflict injury, I ask for forgiveness, I try to reestablish trust, and then I do it all over again. We even number the chemo treatments in cycles, reminding ourselves of time's circularity, the not-so-merry merry-go-round. Along another axis, their course can be seen as a roller coaster: a plunge into toxic effects, an ascent back to baseline, and then another precipitous decline. I learn each patient's pattern as I go, and I try to counsel accordingly. But will Covid-19 deepen the troughs to unfathomable lows? Only time will tell.

Disclosure forms provided by the author are available at NEJM.org.

From the Department of Oncology, Intermountain Healthcare, Murray, UT.

This article was published on April 7, 2020, at NEJM.org.

1. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020; 21:335-7.
2. Xia Y, Jin R, Zhao J, Li W, Shen H. Risk of COVID-19 for cancer patients. Lancet Oncol 2020;21(4):e180.
3. Wang H, Zhang L. Risk of COVID-19 for patients with cancer. Lancet Oncol 2020; 21(4):e181.

DOI: 10.1056/NEJMp2006588