additional pharmacokinetic simulations. This schedule has been demonstrated to provide equivalent exposure, and has been approved by the European Medicines Agency. However, it was rejected by the FDA in February 2020, for reasons unclear to us. Following the arrival of the COVID-19 pandemic, clinicians and institutions have been looking for opportunities to decrease patient visits to the hospital, to limit exposure to SARS-CoV-2. An obvious opportunity was to recommend pembrolizumab at a dosage of 400 mg every 6 weeks, instead of 200 mg every 3 weeks, recognizing that this would be an off-label dosage in the US. Guideline committees at the National Comprehensive Cancer Network issued such off-label guidance in March 2020, stating that “receptor occupancy is considered therapeutic at this dosing schedule.” Subsequently, on April 28, 2020, the FDA issued an accelerated approval for the previously rejected regimen of 400 mg every 6 weeks. The rationale for the initial rejection followed by the subsequent approval remains unclear.

We would argue that there is a better solution: namely, a dosage of 4 mg/kg every 6 weeks, with a cap at 400 mg. Given that the fixed dosing every 6 weeks is based on pharmacokinetic data, we similarly propose weight-based dosing based on pharmacokinetic data. The Canadian Agency of Drugs and Technologies in Health replicated the pharmacokinetic model used by the manufacturer and performed additional simulations. They demonstrated that a dosage of 400 mg every 6 weeks provides adequate trough target engagement even for patients whose weights are higher than average, with occupancy of 97% for patients weighing 100 kg and 96% for those weighing 150 kg. One can therefore infer that this level of trough target engagement is considered acceptable by both the National Comprehensive Cancer Network and the FDA. In the simulations by the Canadian Agency of Drugs and Technologies in Health using 4 mg/kg every 6 weeks in patients weighing 70, 100, and 150 kg, the trough target engagement was approximately 97% for all 3 dosages. We thus suggest that 4 mg/kg, capped at 400 mg, provides target occupancy equivalent to that of the FDA-approved fixed dosage. It is also important to consider that even this dosage is likely to be higher than necessary, recognizing that the manufacturer’s pharmacokinetic simulation demonstrates that 95% trough target engagement is achieved with dosing at 0.8 mg/kg every 3 weeks.

This weight-based dosage is also feasible without vial sharing for most patients. Although pembrolizumab is only available in the US in 100-mg vials, a patient weighing 75 kg or less will need only 300 mg (3 vials), a 25% cost savings. In fact, due to commonly accepted rounding policies (ie, 10%), a patient weighing up to 82.5 kg could receive 300 mg. Therefore, more than half of patients would require only 3 vials instead of 4. Furthermore, closed hospital systems, such as the Veterans Affairs System or Kaiser Permanente, may be willing to institute vial-sharing mechanisms for patients who weigh more than 82.5 kg or less than 67.5 kg. Such hospital systems have a direct incentive to decrease drug expenditure.

This solution would be highly beneficial to individual patients: it would decrease their exposure to SARS-CoV-2, maintain equivalent efficacy, and decrease financial effects for patients who bear a share of the cost. It would also provide a great benefit to society at large. In 2019, worldwide sales of pembrolizumab generated $11 billion for the manufacturer. A significant proportion of this could be saved by health care payers by adoption of a dosage of 4 mg/kg every 6 weeks. Such savings could then be redistributed to other health needs, having a net positive effect on population health. Furthermore, these savings could be used as part of a financial recovery plan for the effect of the COVID-19 pandemic. While we have used pembrolizumab as an example, there is little doubt that the principles used here apply to many checkpoint inhibitors, and indeed to many monoclonal antibodies in therapeutic use.

Opinion

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Distancing Without Isolating—Connection in the Era of COVID-19

Caring for patients with cancer can be difficult at the best of times. The delicate interplay between a complex disease, multidisciplinary management, social barriers, family support, and mental health makes the field of oncology uniquely challenging and rewarding. On March 11, 2020, the World Health Organization declared the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its accompanying illness, coronavirus disease 2019 (COVID-19), a global pandemic. To adequately care for patients, we now must add the pandemic's accompanying medical, social, and economic challenges to the mosaic of obstacles. Although our commitment to curing patients' cancer is unwavering, our focus has undeniably shifted. In the pre–COVID-19 era, we aimed to support patients both medically and emotionally through the safest and most effective treatment possible. Today we may be asking ourselves, “How much can I minimize a patient’s contact with the health care system while still providing quality care?” or “Are we willing to accept a slightly higher risk of toxic effects to minimize a patient’s exposure to the virus?” or importantly, “How can I keep patients from feeling isolated while insisting on their social isolation?”

Many patients feel particularly isolated fighting cancer during a pandemic. This remoteness is enhanced by the environment in which they must navigate the health care system. If their visits are in person, patients are typically asked to present alone, without the support of family or friends as they receive information about their diagnosis, go over adverse effects, or discuss changes to their treatment plan. These interactions are conducted in a large room to facilitate social distancing (at least 6 feet apart), with all parties masked and sometimes gowned—a sterile environment. Waiting rooms are either closed or quiet and austere, with chairs far apart. Patients are screened for symptoms and asked to take their temperature prior to entering the clinic. Although many patients express understanding and gratitude at these measures and are consciously aware of their necessity, the segregation between patients and clinicians is detrimental to a physician’s ability to establish rapport and provide emotional support through social expression and body language.

The prevalence of psychological distress in patients with cancer ranges from 20% to 47% depending on the cancer diagnosis and extent of disease. Patients at increased risk of psychological distress are those with prior psychiatric disorders, depression, substance abuse, severe comorbid illness, or communication barriers, as well as those with social characteristics such as younger age, female sex, and living alone. Psychological distress reduces quality of life and can negatively influence survival. The current COVID-19 outbreak has negatively affected mental health globally, with dramatic increases in anxiety, depression, stress, insomnia, and fear.

Many ambulatory clinicians have appropriately transitioned to telephone or virtual patient encounters to enforce social distancing and comply with shelter-in-place mandates. However, within radiation oncology, even while attenuating treatment as much as possible, many patients continue to require daily visits to the medical center or radiation facility to receive treatment. The authors of this article see the vast majority of breast and gynecologic cancers at our institution; diseases that are, for the most part, curable or controllable. However, over the preceding weeks, we have seen a dramatic increase in psychological distress among the patients in our care. Specific fears they have voiced include wondering if their cancer is being managed appropriately, feelings of isolation, worries about their immune status and risks of contracting COVID-19, concerns about the department continuing to stay open, and even concern about the well-being of their health care clinicians.

Experts around the globe have exhaustively pored over data and held discussions to determine the optimal oncology care while also minimizing the risk of exposure. For clinicians, these guidelines provide a slightly more stable foundation from which to conduct care in a constantly shifting landscape. Patients, unaware of this constant stream of discussion, may feel adrift in a sea of uncertainty or, worse, abandoned by their care team. It is up to us to find the appropriate method of communication that continues to make patients feel supported during a time when they are dealing with multiple layers of stress.

Navigating the needs of women with breast and gynecologic cancers during this time has given us insight into some of the techniques that can be effective (Table). Importantly, when we are limited in our ability to demonstrate care and concern with our usual social interaction, spending extra time in virtual or telephone visits in which we give space for patients to express their anxieties can be invaluable. They often use this time to ask questions about COVID-19 or share fears about their cancer care being lost in the shuffle during the pandemic. It is important to validate and normalize their fears and share concrete information when applicable. Feelings of abandonment may be somewhat mitigated by checking in more frequently with remote methods of communication, such as direct electronic medical record messaging or telephone calls. Calling family members separately or conducting conference calls can promote feelings of inclusiveness and ease the burden of receiving information in isolation. If patients want to continue the conversation with others, many virtual support groups have been established.
COVID-19 has drastically changed the way we practice medicine and will undoubtedly result in permanent shifts both in our medical and general societal interactions. As we start to navigate post-COVID-19 oncology, we are faced with yet another myriad of challenges: assessing the effects of the pandemic on patients with cancer, using what we have learned to guide future treatment techniques, navigating hospital resource utilization, and ensuring adequate preparation for future events, just to name a few. Given oncologists' ability to find delight and meaning in solving complicated problems, we are confident in the ability of our field to successfully rise to the challenge. However, here we draw attention to these early signs of distress to ensure that we do not lose sight of the fundamental need for human connection as we move into a new era of patient care. It remains our duty and privilege to be present for patients, now more than ever.

### Table. Common Distress Themes and Recommendations in Patients With Cancer During the Coronavirus Disease 2019 (COVID-19) Pandemic

<table>
<thead>
<tr>
<th>Distress</th>
<th>Patient reactions</th>
<th>Recommendations</th>
</tr>
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<tbody>
<tr>
<td>Isolation</td>
<td>“I don’t have anyone to talk to about this.”</td>
<td>• Check in more frequently.</td>
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<td></td>
<td>“It feels strange to be on my own during this.”</td>
<td>• Recommend virtual support groups. Include family in telephone/virtual visits if possible.</td>
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<td>Abandonment</td>
<td>“I haven’t met my doctor; we only spoke on the phone.”</td>
<td>• Opt for virtual visits over telephone visits to allow visual connection.</td>
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<td></td>
<td>“I don’t know if my treatment will continue given what’s going on.”</td>
<td>• Allow extra time during visits to listen and provide reassurance.</td>
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<td>Risk of COVID-19</td>
<td>“I am nervous about coming to a medical facility so many times.”</td>
<td>• Share disinfection/social distancing measures the facility has taken.</td>
</tr>
<tr>
<td></td>
<td>“Am I at greater risk because I have cancer?”</td>
<td>• Validate concerns; provide active listening.</td>
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<td>Changes to treatment plan</td>
<td>“How do we know the shorter treatment will work as well?”</td>
<td>• Reiterate constant communication among treatment team, both intramurally and extramurally.</td>
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<td>“Will this delay negatively affect my cancer care?”</td>
<td>• Share data when appropriate.</td>
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<td></td>
<td></td>
<td>• Discuss risks and benefits of changes.</td>
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**REFERENCES**