VIEWPOINT

Weight-Based Dosing of Pembrolizumab Every 6 Weeks in the Time of COVID-19

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The coronavirus disease 2019 (COVID-19) pandemic has shocked the world and caused a period of both economic and medical catastrophe. Two major challenges face the world of medical oncology. Oncologists need to reconsider all of their clinical practices to decrease the risk of exposure of their patients to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Oncologists also need to consider that the world has changed considerably in economic terms. Now, more than ever, we need to assess whether our recommended therapies will cause financial hardship, on both an individual and a societal level. In this article we propose a solution related to the dosing of pembrolizumab that will maintain therapeutic outcomes, decrease detrimental financial effects of treatment, and decrease exposure risk to SARS-CoV-2.

The initial phase 3 trials of pembrolizumab used a dosage of 2 mg/kg every 3 weeks, leading to the first US Food and Drug Administration (FDA) approvals of this dosage in treatment of patients with melanoma and with non–small cell lung cancer. Subsequent trials used a fixed dosage of 200 mg every 3 weeks, with the stated reason being that using a fixed dosage was more convenient. Pharmacokinetic simulations performed by the manufacturer and accepted by the FDA demonstrated pharmacokinetic equivalence, and thus led to retroactive label changes for previously approved indications. However, it was noted that this dosage was higher than necessary. As the average patient with cancer weighs 75 kg, only 150 mg would be required for such a patient. It was estimated that US health care payers could save $0.8 billion annually by switching back to weight-based dosing for patients with programmed cell death ligand 1–positive non–small cell lung cancer receiving pembrolizumab as monotherapy.[1]

This strategy has been established as policy in Canada[2]; however, in other parts of the world, it does not appear to have gained traction, owing to a few different reasons. First, the availability of appropriate vial sizes means that weight-based dosing is logistically challenging. Originally, there were 100-mg and 50-mg vials; however, the 50-mg vials were removed from the US marketplace. There was no incentive in the US to consider vial sharing among patients, as the JW modifier states that the US Centers for Medicare and Medicaid Services will reimburse the prescriber for any leftover drug.[3] As a result, the standard practice in recent years has been to continue with a dosage of 200 mg every 3 weeks.

Recently, the manufacturer of pembrolizumab has sought to gain regulatory approval for a more convenient dosage: 400 mg every 6 weeks. Based on additional pharmacokinetic simulations,[4] 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."[5] 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[6] 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.[2] 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.[2] 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.[6]

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.[7] 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 exemplar, there is little doubt that the principles used here apply to many checkpoint inhibitors, and indeed to many monoclonal antibodies in therapeutic use.

ARTICLE INFORMATION

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