Pembrolizumab Administration Frequency, Dose Exposure, and Toxicity: Is Switching Safe?

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The optimal dosing and administration frequency of immunotherapeutic agents, including immune checkpoint inhibitors (ICIs), remains a controversial issue in oncology. Pharmacokinetic (PK) and pharmacodynamic properties of anti–programmed cell death protein 1/anti–programmed death-ligand 1 monoclonal antibodies are distinct from those of chemotherapeutic agents which follow a typical dose-dependent drug-exposure pattern. As with other monoclonal antibodies, ICIs exhibit a low volume of distribution, low clearance, and long half-life; their clearance is also minimally affected by renal or hepatic impairment.1

Results from the initial phase 1, dose-finding study of pembrolizumab revealed typical PK characteristics with maximum serum target engagement reached with levels of doses greater than or equal to 1 mg/kg every 3 weeks, with robust clinical activity observed at doses of 2 mg/kg every 3 weeks.2 Results from the phase 2/3 KEYNOTE-010 trial revealed no substantial difference in terms of efficacy between pembrolizumab 2 mg/kg and 10 mg/kg every 3 weeks. Similarly, grade 3 to 5 treatment-related adverse events were comparable (at 13% and 16% for the 2 mg/kg and 10 mg/kg cohorts, respectively) suggesting no substantial difference in toxicity according to the dose intensity.3 On the basis of these observations, the initial phase 3 trials of pembrolizumab used a dosage of 2 mg/kg every 3 weeks, leading to the first U.S. Food and Drug Administration approval of this dose in treatment of patients with melanoma and NSCLC.

Fixed flat dosing of ICIs has been evaluated using population PK and exposure-response analyses in modeling/simulation studies. These in silico studies with programmed cell death protein 1/programmed death-ligand 1 inhibitors predicted comparable exposures between flat and traditional body weight-based dosing strategies leading to regulatory approval of fixed dose regimens for nivolumab and pembrolizumab. These findings further confirmed that the efficacy and toxicity of pembrolizumab are not dose dependent, and a fixed dose of 200 mg every three weeks (Q3W) was selected for further clinical development of the agent.

The coronavirus disease 2019 pandemic led to significant modifications in the management of patients with cancer, with an emphasis on reducing the number of visits to the infusion center and maximizing intervals between hospital visits. To this direction, international scientific societies, such as the International Association for the Study of Lung Cancer (available at: https://www.iaslc.org/research-education/iaslcs-guide-covid-19-and-lung-cancer), the American Society for Clinical Oncology,4 and the European Society for Medical Oncology5 developed guidelines for optimal management of patients with cancer during the pandemic and strongly advocated for extended intervals for infusional therapy of patients under specific anticancer treatments, including immunotherapy. In this context, a model-based approach was...
used to compare the exposure of pembrolizumab at the double dose of 400 mg dose every 6 weeks (Q6W) with the Q3W regimen. Of note, this comparative drug-exposure study revealed that the 400 mg Q6W dose had similar predicted exposure as the 200 mg Q3W dose with fewer than 1% of subjects having transiently lower minimum concentration (Cmin), compared with that observed for 200 mg and 2 mg/kg Q3W dosing regimens, suggesting thus a similar target saturation level. On the basis of these data and in light of the pandemic, U.S. Food and Drug Administration approved the new dosing regimen of 400 mg Q3W on April 28, 2020, and this regimen has been widely adopted in daily clinical practice. Similar extended dosing intervals have been approved for other ICIs, such as nivolumab, atezolizumab, and durvalumab.

In the article that accompanies this editorial, Higashiyama et al. used real-world data to evaluate the safety of switching the dose of pembrolizumab to an extended-dose interval, 400 mg Q6W in 45 patients with advanced NSCLC who had been previously treated with pembrolizumab monotherapy at a standard dose of 200 mg Q3W. The authors reported that among the 45 patients, 17 patients (37.8%) developed new or experienced deterioration of existing immune-related adverse events (irAEs), with pneumonitis being the major irAE of concern (24.4%).

To put these data into context for a practicing clinician, it is important to recognize the patterns of observed irAEs among these patients. Of the 11 patients who developed pneumonitis, two patients had pre-existing asymptomatic pneumonitis (grade 1) before switching the dose. In both these patients, pneumonitis worsened to grade 2 after switching to the Q6W regimen, which the authors suggest is related to a “peak-dose” dependent effect. Does the higher Cmax observed with the 400 mg Q6W dose correlate with higher probability for irAEs? We know that this regimen provokes a rapid change in peak concentration and that the predicted Cmax for 400 mg Q6W was substantially (approximately 65%) lower than the 10 mg/kg Q2W dose, but overall similar to the 200 mg and 2 mg/kg Q3W doses. The effect of the higher peak concentration levels achieved with this regimen on the probability for new or worsening irAEs remains to be clarified, and at this time, it is impossible to predict whether these patients would have developed a higher grade of irAEs even without the dose/interval change.

Two patients who developed pneumonitis after switching had received tyrosine kinase inhibitors for oncogene-addicted disease as the immediate previous treatment. In these cases, we cannot assume that the pneumonitis was truly associated with just the switching of pembrolizumab dose, as previous use of tyrosine kinase inhibitors with subsequent introduction of ICIs has been associated with higher rates of irAEs, including pneumonitis. In addition, it is known that there are ethnic differences in the pattern of toxicity after ICI administration, with higher rates of pneumonitis and interstitial lung disease reported in Japanese patients compared with the non-Japanese population. Indeed, in this study, from a single center in Japan, the rate of irAEs was higher compared with previous reports, as was the discontinuation rate in the 400 mg Q6W level (26.7%), suggesting there may be inherent ethnic variations at play.

Other important questions center around management of patients with clinically significant irAE—Should these patients be subsequently treated with the original dose of 200 mg Q3W? and Is resumption of the Q6W dose regimen safe? Although the study does not provide clear guidance on management of dosing schedule in these patients, it is reassuring to find that four patients were rechallenged with pembrolizumab either at the previous dose of 400 mg Q6W (two patients) or at the original dose of 200 mg Q3W (two patients).

Although these results are intriguing, it should be emphasized that this was a single institution study evaluating a small patient cohort in a retrospective fashion. Assessment of irAEs was subjective, largely dependent on the treating physician’s clinical practice. The follow-up for the occurrence of new irAEs was short (within three cycles after dose switch), limiting thus the detection of irAEs that tend to occur later in the course of treatment, such as endocrinopathies. Moreover, the reasons for switching the dose regimen are unclear and the decision for switch was rather arbitrary depending on the treating physician’s judgment. This aspect becomes more relevant considering that five patients had already experienced irAEs before switching, including one case of grade 2 adrenal dysfunction. Finally, data on resolution of the irAEs and the guidelines used for their management are unclear, because some patients did not receive steroids according to current protocols.

Extended-interval dose strategies for ICIs have been allowed for greater flexibility and convenience to both patients and their caregivers. This strategy has been extremely useful during the coronavirus disease 2019 pandemic, as a means to continue patients on therapy while maximizing safety and reducing the risk of transmission. This study raises several important, but yet unanswered questions. It is clear that only a prospectively designed randomized clinical trial comparing the two dose regimens balanced for factors of inherent bias can definitely address these questions. Integration of biomarkers such as circulating tumor-free DNA and others may help guide the optimal timing for switch from standard to extended-interval regimens. Until then, clinical decisions should be individualized, including the
history of autoimmune disease, the tolerance of the original 200 mg Q3W regimen, and patient preference. In clinical practice, close monitoring of patients switching from the one dose regimen to the other and patient education to identify irAEs and seek medical advice in a timely manner are imperative to ensure patient safety.

CRediT Authorship Contribution Statement

Giannis Mountzios, Charu Aggarwal: Conceptualization, Data collection, Writing.

References


