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EDITORIAL

Alternative dosing regimens for atezolizumab: right dose, wrong frequency

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Abstract

The population pharmacokinetics of atezolizumab demonstrate that the trough concentrations are well above the putative target of 6 µg/ml. Thus, alternative dosing schedules are indeed of interest, focusing on reducing the frequency to allow greater patient convenience and reduced costs.

Keywords Pharmacoeconomics · Atezolizumab · Pharmacokinetics · Schedule

Atezolizumab, a PD-L1 inhibitor, is now approved for use in patients with non-small cell lung cancer (NSCLC), small cell lung cancer, urothelial carcinoma (UC), and triple-negative breast cancer. As with other checkpoint inhibitors, initial studies used weight-based dosing, prior to switching to a strategy of fixed dosing for all patients. The paper in this issue of *Cancer Chemotherapy and Pharmacology* by Morrissey and colleagues exemplifies the use of modeling and simulation to explore the potential clinical consequences of dose and schedule changes [1]. Notably, this approach has already been accepted by global regulatory authorities to support label changes for nivolumab and pembrolizumab.

The authors developed exposure-efficacy and exposure-safety models for NSCLC and UC in conjunction with a previously developed population pharmacokinetic model, to assess the hypothetical impact of schedule change on efficacy and toxicity. Their conclusion that the schedule does not matter as long as the average weekly dose is 400–420 mg is not surprising, given that the serum drug concentrations were far in excess of the target concentration.

However, in our opinion, they have asked the wrong question. They did not simulate other alternative schedules, those that use lower dosages or less frequent dosing, the strategy of interventional pharmacoeconomics [2]. While such regimens may not be in the interest of atezolizumab's manufacturer (Genentech), they are certainly in the interest of patients and payers, as long as the efficacy is expected to be the same. This approach of reduced intensity immunotherapy has previously been suggested for nivolumab [3], however the magnitude of opportunity appears to be even greater for atezolizumab. Genentech authors have previously suggested that the target trough concentration is 6 µg/ml, based in part on the assumption that atezolizumab would be coadministered with bevacizumab, which would decrease tumor penetration by at least 30% [4]. The implication of this is that in the absence of bevacizumab, the target trough concentration would be at least 30% lower, approximately 4.2 µg/ml. Notably, complete saturation of PD-L1 in mouse blood was achieved at serum concentrations ≥ 0.5 µg/ml.

The phase 1 dose escalation study evaluated doses of 0.01–20 mg/kg every 3 weeks, and activity was observed at doses as low as 1 mg/kg [5, 6]. Even patients at low doses had trough concentrations at or near the target concentration after the first dose. For example, the mean cycle 1 trough concentration (C_{min}) was 3.8 µg/ml at 1 mg/kg, and 12.2 µg/ml at 3 mg/kg. Furthermore, the accumulation ratio on the 3-weekly schedule is approximately 1.9, suggesting that the mean steady-state C_{min} exceeds the target trough at 1 mg/

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kg. Thus, the preclinical and pharmacokinetic data alone strongly support the hypothesis that the standard 1200 mg dose administered every 3 weeks is too high, given that the steady-state C_{min} at higher doses exceeds 100 µg/ml.

While exposure–response relationships are often apparent for therapeutic monoclonal antibodies due to high clearance being a marker for cancer cachexia and poor outcomes, such relationships were not reported by Morrissey and colleagues [1]. In the exposure–response analyses, it is evident that with the lowest quartile having a mean cycle 1 C_{min} of approximately 40 µg/ml, one could be very confident that therapeutic concentrations were maintained. With regard to the steady-state data, the exposure is far higher than necessary. The mean steady-state C_{min} for all of their dosing options are 182–238 µg/ml (90% prediction interval 89–443 µg/ml). The high accumulation ratio may be partially related to time-dependent clearance, as previously identified for multiple similar drugs [7–9]. This feature of time-dependent clearance provides particular justification for dose reductions in responding patients.

Thus, there is immense potential to reduce the prescribing costs of atezolizumab through application of existing clinical pharmacology data, supplemented by prospective interventional pharmacoeconomic trials. The simplest approach would aim to reduce the average weekly dose. We would advocate using a standard 840 mg dose, but with a dosing interval far greater than the recommended interval of 2 weeks.

As a more elegant alternative, we would propose the use of therapeutic drug monitoring (TDM) to individualize the frequency of dosing, with the goal of maintaining a therapeutic trough concentration. While a C_{min} of ≥ 6 µg/ml has been previously suggested as a conservative target based on preclinical studies [4], also assuming bevacizumab co-administration, this has not yet been validated clinically. Once these clinical studies are completed, TDM could be a very viable option to guide dosing frequency. Not only would this strategy of TDM reduce use of scarce healthcare resources, it would also provide increased convenience for patients, requiring fewer visits to the infusion suite. Confirmation that the trough is in the therapeutic range would provide confidence to patients and physicians that the alternative dosing regimen is likely to have comparable efficacy to a labeled dosing regimen. An alternative, and even cheaper, method of dosing individualization could use albumin changes as a surrogate for clearance changes. This approach has been previously investigated for durvalumab. [10] In an era of both personalized medicine and budget constraints, the dosing of atezolizumab provides great opportunity.

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Compliance with ethical standards

Conflict of interest M.J.R. reports grants from AbbVie, personal fees from Aptevo, personal fees from Cyclacel, other from BeiGene, grants from Dicerna, personal fees from multiple generic pharmaceutical companies, grants from Genentech, personal fees from Pneuma Respiratory, outside the submitted work; and Co-founder and Director, Value in Cancer Care Consortium (Vi3C, www.vi3c.org). D.A.G. declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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