Infusion-related reactions with administration of avelumab: mild and manageable side effects

James L. Gulley[1], Karen Kelly[2]

[1]Genitourinary Malignancies Branch and Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; [2]University of California-Davis, Comprehensive Cancer Center, Sacramento, CA, USA

Correspondence to: James L. Gulley, MD, PhD. Genitourinary Malignancies Branch and Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Building 10, Room 13N240, Bethesda, MD 20892-1750, USA. Email: gulleyj@mail.nih.gov.

Response to: Tanvetyanon T. Avelumab: a promising PD-L1 inhibitor for lung cancer (with inconvenient infusional reactions). Transl Cancer Res 2017;6:S1061-3.

Immune checkpoint inhibitors have demonstrable clinical activity in various advanced malignancies. Avelumab— a human anti-programmed death-ligand 1 (anti-PD-L1) monoclonal antibody that inhibits signaling through the programmed death 1 (PD-1) immune checkpoint— has shown clinical activity in patients with recurrent or metastatic non-small cell lung cancer (NSCLC) (1), refractory metastatic urothelial carcinoma (mUC) (2), refractory metastatic Merkel cell carcinoma (mMCC) (3,4), and other advanced cancers. Avelumab has been approved by the United States Food and Drug Administration for the treatment of patients with mMCC and locally advanced or mUC who have disease progression during or following platinum-containing chemotherapy (5). In addition, the European Medicines Agency Committee for Medicinal Products for Human Use has recommended its approval for the treatment of patients with mMCC.

Infusion-related reactions (IRRs) are a commonly reported side effect of treatment with monoclonal antibody therapies (e.g., trastuzumab, rituximab, cetuximab) and chemotherapy (e.g., taxanes) (6,7). In addition to avelumab, other checkpoint inhibitors are also associated with IRRs during treatment, and their incidence and management are included in the prescribing information for each of these medications (5,8-11). The majority of IRRs associated with avelumab are low grade (i.e., grade 1/2), do not result in treatment discontinuation, and have very straightforward management (1,3,12). Most reactions are mild, occur during drug administration or shortly thereafter, and have been rarely observed after the first 4 infusions of avelumab, with the majority occurring at initial infusion (12). Following grade 1 or 2 events, IRRs can be managed by slowing the infusion rate or interrupting and restarting at a temporarily slower rate—but not reducing the overall dose of avelumab—and by administering supportive medications, allowing oncologists to continue giving avelumab to patients who have advanced malignancies and limited treatment options. Using a premedication regimen of antihistamine and acetaminophen prior to the first 4 infusions is recommended in the avelumab prescribing information and is based on experience from clinical trials, in which most patients received diphenhydramine, an H1-antihistamine (5). Clinical practice experience suggests that other selective H1-receptor antagonists, such as fexofenadine or cetirizine, may also be effective and have a less sedating effect. In some cases, premedication with low-dose corticosteroids has also been used to effectively mitigate the incidence of IRRs (6). In our clinics, we have successfully employed such measures while treating patients with avelumab and with other checkpoint inhibitors. Experienced oncology physicians and nurses observing patients during avelumab infusions are well prepared to

promptly and efficiently recognize and manage IRRs.

Cross-study comparisons of IRRs should be interpreted with caution. In Gulley *et al.* (1), IRRs were identified using a composite definition that included IRR, drug hypersensitivity, and anaphylactic reaction—or related symptoms, including fever, chills, rigors, pyrexia, and flushing—that occurred within 1 day of infusion and resolved within 2 days of infusion. Other studies used in the comparison made by Tanvetyanon (13) articulate no clear definition of IRR (14) or apply one limited to 1 or 2 adverse-event terms, including hypersensitivity/infusion reaction (15), infusion reaction (16), or IRR (8). In addition, study design, dosing schedules, and patient characteristics vary considerably in the studies cited by Tanvetyanon, which included trials in NSCLC and mUC (1,8,11,15,16). The expanded, comprehensive definition of an IRR in the large, multicohort JAVELIN Solid Tumor study (NCT01772004) and other clinical trials of avelumab has been used consistently, and the data show that, regardless of tumor type, IRRs associated with avelumab treatment are mostly temporary, low grade, and rarely lead to permanent discontinuation (in up to 2.0% of patients) (5,12).

Avelumab is unique among approved PD-1 or PD-L1 immune checkpoint inhibitors in that it retains an intact Fc region and is capable of inducing antibody-dependent cell-mediated cytotoxicity (ADCC), as shown in *in vitro* studies of human cells (17-19). Although the overall contribution of ADCC to the clinical activity of avelumab is still being investigated, ongoing phase 1/2 combination studies will investigate its potential to improve the clinical activity of avelumab monotherapy in various tumor types.

Differences in disease (i.e., NSCLC *vs.* mUC), number of prior therapies, eligibility criteria, stratification, dosing schedule, and, most importantly, the definition of an IRR make drawing conclusions from interstudy comparisons a challenge. The compelling clinical activity of avelumab in these difficult-to-treat diseases far outweighs the modest inconvenience of low-grade, easy-to-manage IRRs. Oncologists and oncology nurses experienced with administering chemotherapy and targeted therapies to patients with cancer are well positioned to use avelumab and other approved immune checkpoint inhibitors safely and appropriately in the clinical setting.

Acknowledgments

Footnote

References

1. Gulley JL, Rajan A, Spigel DR, et al. Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial. Lancet Oncol 2017;18:599-610.
2. Apolo AB, Infante JR, Balmanoukian A, et al. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a

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multicenter, Phase Ib study. J Clin Oncol 2017;35:2117-24.

3. Kaufman HL, Russell J, Hamid O, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 2016;17:1374-85.

4. Kaufman HL, Russell JS, Hamid O, et al. Durable responses to avelumab (anti-PD-L1) in patients with Merkel cell carcinoma progressed after chemotherapy: 1-year efficacy update. Cancer Res 2017;77:abstr CT079.

5. Bavencio (avelumab) injection. Darmstadt, Germany: Merck KGaA; 2017.

6. Vogel WH. Infusion reactions: diagnosis, assessment, and management. Clin J Oncol Nurs 2010;14:E10-21.

7. Chung CH. Managing premedications and the risk for reactions to infusional monoclonal antibody therapy. Oncologist 2008;13:725-32.

8. Imfinzi (durvalumab) injection. Wilmington, Delaware: AstraZeneca Pharmaceuticals LP; 2017.

9. Opdivo (nivolumab) injection. Princeton, New Jersey: Bristol-Myers Squibb Company; 2017.

10. Keytruda (pembrolizumab). Whitehouse Station, New Jersey: Merck & Co, Inc.; 2017.

11. Tecentriq (atezolizumab) injection. South San Francisco, California: Genentech, Inc.; 2017.

12. Kelly K, Infante JR, Taylor MH, et al. Safety profile of avelumab in patients with advanced solid tumors: a JAVELIN pooled analysis of phase 1 and 2 data. J Clin Oncol 2017;35:abstr 3059.

13. Tanvetyanon T. Avelumab: a promising PD-L1 inhibitor for lung cancer (with inconvenient infusional reactions). Transl Cancer Res 2017;6:S1061-3.

14. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837-46.

15. Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 2017;376:2415-26.

16. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375:1823-33.

17. Boyerinas B, Jochems C, Fantini M, et al. Antibody-dependent cellular cytotoxicity activity of a novel anti-PD-L1 antibody avelumab (MSB0010718C) on human tumor cells. Cancer Immunol Res 2015;3:1148-57.

18. Fujii R, Friedman ER, Richards J, et al. Enhanced killing of chordoma cells by antibody-dependent cell-mediated cytotoxicity employing the novel anti-PD-L1 antibody avelumab. Oncotarget 2016;7:33498-511.

19. Heery CR, O'Sullivan-Coyne G, Madan RA, et al. Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial. Lancet Oncol 2017;18:587-98.