Use of immortal time within survival analysis

To the Editor: The development of programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) immunotherapy has revolutionized the life-extending power of oncologic treatment.[1] Both agents are associated with many dermatologic adverse events, including dermatitis.[2] We read with interest the recently published article by Min Lee et al.[3] This study concluded that developing biopsy-proven dermatitis ≤3 months posttreatment with PD-1/PD-L1 was a strong positive predictor of overall survival and progression-free survival over patients who do not develop dermatitis. After carefully examining the study's methodology, we wish to warn readers about the what is now called "immortal time" error that appeared in this article.[4]

Min Lee et al[3] state that "patients who experienced a dermatitis after initiation of PD-1/PD-L1 inhibitor and up to 3 months after the last PD-1/PD-L1 inhibitor dose" were considered to be of the case cohort. Controls were "patients who did not have any…dermatitis…after initiation of PD-1/PD-L1 inhibitor."[3] There was no data distribution of follow-up in the 2 cohorts. Comparison of the overall survival and progression-free survival between the 2 cohorts was performed using the Kaplan–Meier method. This methodology would be appropriate if the presence or absence of dermatitis occurred at day 0 (ie, start of "time") for Kaplan–Meier analysis. Unfortunately, this was not the case, because all patients were dermatitis-free on day 0 because developing dermatitis is a time-dependent covariate in this study. This means that only with the passage of time on treatment do some patients move into the dermatitis group. In addition, analyzing the survival of patients who develop dermatitis ≤3 months after receiving PD-1/PD-L1 treatment confers "immortal time" to the dermatitis cohort. This is not appropriate. If the patient has survived ≤3 months from their first dose of PD-1/PD-L1 treatment, they have already survived for ≤3 months by the fact that they have been on the current treatment. These patients are in effect immortal during the time it took them to develop dermatitis, for they were only included in the case cohort because they had survived for long enough to develop the dermatitis. It is unclear when (and indeed if) the control group was assessed for dermatitis.

Similar issues have been noted in other studies.[4,5] William Farr, an epidemiologist, had also warned about this error as early as the 1840s. He warned that crediting the years of health required to reach military officer ranking by the time he/she dies, or censor date, exaggerates any longevity-extending benefits of reaching the rank.[4] In this example, those individuals were not awarded their ranks because they were healthy, but rather they needed to be healthy and alive for sufficiently long periods of time to be able to reach the ranks.

We recommend that the authors re-evaluate the data using an appropriate statistical methodology to be able to account for the time-dependent nature of the status of developing dermatitis.

Linda Chan, MBBS,[a] Karen Byth, PhD,[b,c] and Pablo Fernandez-Penas, MD, PhD[a,b]

Department of Dermatology[a] and the Research and Education Network,[c] Westmead Hospital, Sydney, and Sydney Medical School,[b] The University of Sydney, Sydney, Australia

Reprint requests: Linda Chan, MBBS, Department of Dermatology, Westmead Hospital, Hawkesbury Rd and Darcy Rd, Westmead, NSW 2145, Australia.

E-mail: lindachan.health@gmail.com

REFERENCES

1. Gong J, Chehrazi-Raffle A, Reddi S, Salgia R. Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: a comprehensive review of registration trials and future considerations. *J Immunother Cancer*. 2018;6:8.
2. Hwang SJ, Carlos G, Wakade D, et al. Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma: a single-institution cohort. *J Am Acad Dermatol*. 2016;74:455-461.e1.
3. Min Lee CK, Li S, Tran DC, et al. Characterization of dermatitis after PD-1/PD-L1 inhibitor therapy and association with multiple oncologic outcomes: a retrospective case-control study. *J Am Acad Dermatol*. 2018;79:1047-1052.
4. Hanley JA, Foster BJ. Avoiding blunders involving 'immortal time'. *Int J Epidemiol*. 2014;43:949-961.
5. Hwang SJ, Byth K, Fernandez-Penas P. Time-dependent measurement of adverse events. *JAMA Dermatol*. 2015;151:1392.