Editorial

To surrogate or not surrogate: an ancient dilemma without a happy ending

Giandomenico Roviello

Department of Health Sciences, University of Florence, Florence, Italy

Correspondence to: Giandomenico Roviello, MD. Department of Health Sciences, University of Florence, Viale Pieraccini, 6, 50139 Florence, Italy. Email: giandomenicoroviello@hotmail.it.

Comment on: Haslam A, Hey SP, Gill J, *et al.* A systematic review of trial-level meta-analyses measuring the strength of association between surrogate end-points and overall survival in oncology. Eur J Cancer 2019;106:196-211.

Received: 06 February 2019; Accepted: 18 February 2019; Published: 12 March 2019.

doi: 10.21037/jhmhp.2019.02.01

View this article at: http://dx.doi.org/10.21037/jhmhp.2019.02.01

Haslam *et al.* performed an analysis of surrogate validation studies (1), in order to evaluate the strength of correlation between overall survival (OS) and surrogate markers. The analysis included 78 studies that according the inclusion criteria were meta-analyses of randomised controlled trials that investigated the validation as surrogate endpoint for survival of progression free survival or tumour response rate. Although the most part of the studies involved metastatic setting of disease, about one quart of the studies reported other setting such as adjuvant, neoadjuvant or immunotherapy. The criteria of the Institute of Quality and Efficiency in Health Care (2) and adapted by Prasad *et al.* (3) has been used to evaluate the strength of association between surrogate endpoints and OS. According this criterion, three levels of correlation has been adopted: low, medium or high according the value of r ($\leq$0.7; >0.7 to <0.85 and $\geq$0.85, respectively). About the 40% of studies reported low correlation. In regard of the 4 studies that involved immunotherapy, no high correlation has been observed and low was the correlation of 3 studies. Then, the authors concluded the surrogate endpoints have generally a low or moderate correlation with OS.

The National Institutes of Health (USA) defines surrogate endpoint as "a biomarker intended to substitute for a clinical endpoint". Surrogate endpoints may include biomarkers, behavioural/cognitive scores, radiological data or time to events. In oncological field, the surrogate endpoints should correlate with OS, therefore, both progression free survival and tumour response rate may be ideal surrogate endpoints in oncology, because they should allow lesser expensive and quicker studies. Unfortunately, the study by Haslam et al doesn't validate the use of surrogate endpoints in medical oncology. It should speculate that progression free survival or tumour response rate failed the surrogacy for survival because of they are not cancers specific or drug-correlated. For example, decrease in serum prostate-specific antigen (PSA) value is universally considered a valid surrogate for survival in patients with prostate cancer (4,5); PD-L1 expression has been used as a selective criterion for pembrolizumab treatment of patients with non-small cell lung cancer (NSCLC) and rate of hypertension is historically related with efficacy during anti-angiogenic agents (6). All these data highlight the need of patient's selection with selective biomarkers to guide treatment selection.

During the years, several anti-cancer drugs have been approved on the basis of successful trials with surrogate endpoints for OS (7,8). However, this approach raises several issues because successful phase 2 studies don't translate in positive results on survival in further phase III or post-market studies (7,9,10). This speech is particularly true with novel immunotherapeutic agents, in fact, as reported by Haslam *et al.*, based on a surrogate end-points, pembrolizumab received several approvals (11). However, immunotherapy has a well-known history of poor correlations between surrogate markers and OS (12-14).

This last may due to the pseudo-progression that is a unique event that characterizes the pattern of response and progression of novel immunotherapy compared with those of conventional chemotherapy or biological/molecular

targeted therapies.

In conclusion, there is the need to identify surrogate endpoints that correlate with OS, however, several oncological drugs are approved with the use of surrogate markers for survival, therefore caution it should be used.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Jianrong Zhang (MPH Candidate, George Warren Brown School; Graduate Policy Scholar, Clark-Fox Policy Institute, Washington University in St. Louis, St. Louis, USA).

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jhmhp.2019.02.01). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Haslam A, Hey SP, Gill J, et al. A systematic review of trial-level meta-analyses measuring the strength of association between surrogate end-points and overall survival in oncology. Eur J Cancer 2019;106:196-211.
2. Nasser M, Sawicki P. Validity of surrogate endpoints in oncology. Executive summary of rapid report A10-05, Version 1.1. Institute for quality and efficiency in health care, 2011.
3. Prasad V, Kim C, Burotto M, et al. The Strength of Association Between Surrogate End Points and Survival in Oncology: A Systematic Review of Trial-Level Meta-analyses. JAMA Intern Med 2015;175:1389-98.
4. Roviello G. Role of PSA response as a marker for efficacy of patients with castration-resistant prostate cancer treated with novel hormonal therapies. Int J Biol Markers 2018;33:132-3.
5. Francini E, Petrioli R, Rossi G, et al. PSA response rate as a surrogate marker for median overall survival in docetaxel-based first-line treatments for patients with metastatic castration-resistant prostate cancer: an analysis of 22 trials. Tumour Biol 2014;35:10601-7.
6. Roviello G, Corona SP, Multari AG, et al. Association between ramucirumab-related hypertension and response to treatment in patients with metastatic gastric cancer. Oncotarget 2018;9:22332-9.
7. Kim C, Prasad V. Cancer Drugs Approved on the Basis of a Surrogate End Point and Subsequent Overall Survival: An Analysis of 5 Years of US Food and Drug Administration Approvals. JAMA Intern Med 2015;175:1992-4.
8. Downing NS, Aminawung JA, Shah ND, et al. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. JAMA 2014;311:368-77.
9. Zettler M, Nabhan C. Fulfillment of Postmarketing Requirements to the FDA for Therapies Granted Oncology Indications Between 2011 and 2016. JAMA Oncol 2018;4:993-4.
10. Beaver JA, Howie LJ, Pelosof L, et al. A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics: A Review. JAMA Oncol 2018;4:849-56.
11. US Food and Drug Administration. KEYTRUDA (pembrolizumab) label. In: Services US department of health and human services. MD: Silver Springs, 2018. Available online: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm526430.htm
12. Roviello G, Andre F, Venturini S, et al. Response rate as a potential surrogate for survival and efficacy in patients treated with novel immune checkpoint inhibitors: A meta-regression of randomised prospective studies. Eur J Cancer 2017;86:257-65.
13. Ritchie G, Gasper H, Man J, et al. Defining the Most Appropriate Primary End Point in Phase 2 Trials of Immune Checkpoint Inhibitors for Advanced Solid Cancers: A Systematic Review and Meta-analysis. JAMA Oncol 2018;4:522-8.

14. Kaufman HL, Schwartz LH, William WN Jr, et al. Evaluation of classical clinical endpoints as surrogates for overall survival in patients treated with immune checkpoint blockers: a systematic review and meta-analysis. J Cancer Res Clin Oncol 2018;144:2245-61.

doi: 10.21037/jhmhp.2019.02.01
Cite this article as: Roviello G. To surrogate or not surrogate: an ancient dilemma without a happy ending. J Hosp Manag Health Policy 2019;3:6.

