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ORIGINAL ARTICLE

Strength of Validation for Surrogate End Points Used in the US Food and Drug Administration's Approval of Oncology Drugs

Chul Kim, MD, MPH, and Vinay Prasad, MD, MPH

Abstract

Objective: To determine the strength of the surrogate-survival correlation for cancer drug approvals based on a surrogate.

Participants and Methods: We performed a retrospective study of the US Food and Drug Administration (FDA) database, with focused searches of MEDLINE and Google Scholar. Among cancer drugs approved based on a surrogate end point, we examined previous publications assessing the strength of the surrogate-survival correlation. Specifically, we identified the percentage of surrogate approvals lacking any formal analysis of the strength of the surrogate-survival correlation, and when conducted, the strength of such correlations.

Results: Between January 1, 2009, and December 31, 2014, the FDA approved marketing applications for 55 indications based on a surrogate, of which 25 were accelerated approvals and 30 were traditional approvals. We could not find any formal analyses of the strength of the surrogate-survival correlation in 14 out of 25 accelerated approvals (56%) and 11 out of 30 traditional approvals (37%). For accelerated approvals, just 4 approvals (16%) were made where a level 1 analysis (the most robust way to validate a surrogate) had been performed, with all 4 studies reporting low correlation ($r \leq 0.7$). For traditional approvals, a level 1 analysis had been performed for 15 approvals (50%): 8 (53%) reported low correlation ($r \leq 0.7$), 4 (27%) medium correlation ($r > 0.7$ to $r < 0.85$), and 3 (20%) high correlation ($r \geq 0.85$) with survival.

Conclusions: The use of surrogate end points for drug approval often lacks formal empirical verification of the strength of the surrogate-survival association.

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The US Food and Drug Administration (FDA) may grant oncology drugs either accelerated (provisional) (AA) or traditional (full) (TA) marketing approval.[1] Accelerated approvals are given based on a surrogate end point that is "reasonably likely to predict" true clinical efficacy, ie, survival or quality of life.[2-4] Traditional approvals are granted when a drug demonstrates "a longer or better life or a favorable effect on an established surrogate for a longer or better life."[4] Surrogate end points, thus, play a prominent role in oncology drug approvals, with the strength of the surrogate end point guiding the pathway of approval.

When relying on surrogates to guide clinical and regulatory decisions, it is important that the surrogate-survival correlation is robust to avoid the approval of toxic drugs with no benefit. Bevacizumab received AA in 2008 based on data that it markedly improved progression-free survival (PFS).[5] However, by 2011, that approval was withdrawn when multiple studies found that the drug did not improve overall survival (OS) and carried toxicity and that gains in PFS were smaller than initially appreciated.[6] In retrospect, the approval and subsequent withdrawal of bevacizumab in metastatic breast cancer is not surprising given that multiple validation studies found that this specific surrogate-survival association is weak.[7]

The validation of surrogate end points in oncology is an increasingly important field, with different statistical methods used.[8-12] We favor a clear and simple hierarchy to grade the strength of surrogate-survival correlations.[7,13] In this model, level 3—the lowest level—requires the surrogate-survival correlation to be only biologically plausible. Level 2

From the Medical Oncology Service, National Cancer Institute, National Institutes of Health, Bethesda, MD (C.K.); and Department of Medicine, Division of Hematology Oncology/ Knight Cancer Institute, Oregon Health & Science University, Portland (V.P.).

and level 1 analyses require clinical data. Although level 2 analysis shows that the surrogate is associated with the final outcome across groups, level 1 analysis addresses the clinically relevant question of whether improving the surrogate end point is associated with improvements in survival across many randomized studies. Typically, regression analysis is performed in level 1 studies. The *x* coordinate reflects the change in surrogate end point, and the *y* coordinate reflects the change in final end point. Correlation coefficients (*r*) closer to 1 signify stronger associations. As such, the validation of surrogate-survival associations in oncology exists along an established hierarchy.

We set out to characterize the nature of FDA approvals in oncology from 2009 through 2014. Specifically, what percentages of approvals were accelerated and traditional? Among TAs, what percentage were made based on a surrogate end point? For all approvals granted on the basis of surrogates, what is the documented strength of the surrogate-survival association? Finally for drugs approved based on surrogates, have subsequent trials demonstrated improvements in survival or quality of life? In short, we set out to empirically describe the strength of evidence for 6 years of FDA cancer drug approvals.

METHODS

Data Source

The FDA provides a record of hematology and oncology drug approvals and safety notifications on their website (http://www.fda.gov/Drugs/InformationOnDrugs/ucm279174.htm) and in related links. Each relevant webpage was downloaded and is provided in the Supplemental Figure 1 (available online at http://www.mayoclinicproceedings.org). Further information for each approval was obtained from the Drugs@FDA website, which includes information regarding the approval of new oncology drugs as well as expanded indications for currently approved drugs, date of approval, basis of approval, and a summary of the clinical review that supported the approval.

Study Sample

We identified all oncology drugs approved by the FDA between January 1, 2009, and December 31, 2014, the last complete year at the time of this investigation. Oncology drugs were approved based on improvements in OS or one of the following surrogate end points: improvements in disease response rate (eg, hematologic, pathologic, or tumor response) or delay in progression (eg, improved PFS or recurrence-free survival). We included data on new oncology drugs and on new indications for previously approved oncology drugs.

End Points Extracted

We ascertained the total number of AAs and TAs. We noted the efficacy end point leading to approval. When drugs were approved on the basis of improvement in OS or quality of life—measures of patient-centered benefit—we performed no further investigation. When drugs were approved based on a surrogate end point, we investigated formal analyses of the surrogate-survival correlation and whether subsequent publications have found an OS benefit.

Literature Search

We sought to ascertain the strength of the surrogate-survival correlation. In other words, as the criteria for AA and TA based on surrogates are "reasonably likely to predict" and "established," respectively, we sought to evaluate the practical meaning of these terms.

For each surrogate drug approval, we performed a focused review of the literature to identify available surrogate-survival association studies. Surrogate association studies are widely performed in oncology to assess the strength of the surrogate end points.[14] These studies are often meta-analyses of randomized controlled trials conducted in the same setting as the particular indication of the drug approval. For example, if one wants to know whether PFS correlates with OS in metastatic castrate-resistant prostate cancer, one begins by collecting all randomized controlled trials in this setting. Then one plots whether the hazard ratio or change in PFS (*x* coordinate) predicts the hazard ratio or change in OS (*y* coordinate). Regression analysis is conducted across trials to demonstrate the general correlation between the surrogate and survival. For each specific surrogate drug approval identified, we performed a review of the literature to locate such analyses. Multiple searches were performed, and all the search terms used and databases searched are listed in Supplemental Table 1 (available online

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