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Chart review versus an automated bioinformatic approach to assess real-world crizotinib effectiveness in ALK-positive NSCLC

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INTRODUCTION

In 2009, the Health Information Technology for Economic and Clinical Health Act allocated between $2 million and $10 million for each hospital that practices meaningful use of electronic health records (EHRs).[1] This incentive was intended to increase the adoption rates of medical records across the country and make computer charts the standard for data storage. The oncology community recognized the significant potential of electronic databases not only for the treatment of patients but also for furthering the field through research. An emerging initiative known as Rapid Learning Healthcare System aims to aggregate data from the vast number of nonclinical trial patients treated with routine care to derive results on the basis of real-world data.[2] In 2013, the building of ASCO's Rapid Learning Healthcare System, Cancer LinQ, was approved. Cancer LinQ is not simply a

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AUTHOR CONTRIBUTIONS

Conception and design: Nam Bui, Joel W. Neal
Provision of study material or patients: Nam Bui, Douglas Wood, Heather A. Wakelee, Joel W. Neal
Collection and assembly of data: All authors
Data analysis and interpretation: Nam Bui, Solomon Henry, Heather A. Wakelee, Joel W. Neal
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Nam Bui
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medical database or registry; it acts as a virtual consultant that draws data from across multiple databases (including EHRs, published literature, and molecular science databases) to derive optimal clinical decisions for a particular patient.

In this budding age of computational mining, there is an immense amount of clinical data ripe for extraction from the EHR. One problem with relying on evidence from prospective clinical trials is that it represents a highly selected population that may not be generalizable to patients with cancer as a whole. Using data from EHRs for real-world outcomes can dramatically increase the number of evaluated patients and observed outcomes. However, there are some problems with this approach. One is that data are often stored as free text rather than discrete database variables in clinicians' notes, making abstraction difficult. Second, clinical trial metrics to determine response and progression are usually based on radiographic assessment, which cannot be easily automated.

In this pilot study, we used a chart-mining algorithm to evaluate a cohort of patients with non–small-cell lung cancer (NSCLC) with anaplastic lymphoma kinase (ALK) translocations treated with crizotinib. Rearrangements in the ALK gene have been found to encode fusion proteins that are oncogenic drivers in a subset of approximately 3% of patients with NSCLC.[3] The ALK tyrosine kinase inhibitor crizotinib demonstrated superiority over chemotherapy in two phase III clinical trials,[4,5] establishing it as standard of care for patients with ALK translocation. We analyzed the outcomes of all patients with ALK-positive NSCLC treated at our institution between 2007 and 2013 who received crizotinib as part of their treatment course. We evaluated whether a computational algorithm could search electronic charts with comparable efficacy to manual curation with regard to solely crizotinib therapy. To deal with the heterogeneity of patient chart notation, we primarily analyzed the medication order tables. To approximate progression-free survival, we used the real-world surrogate of time on treatment (TOT), which is defined as start of treatment date to end of treatment date. This avoided determination of radiographic assessment, while potentially also serving as a similar surrogate for clinical benefit, because single-agent therapy in lung cancer is usually continued as long as patients are stable and then then discontinued at the time of progression.

MATERIALS AND METHODS

Patients

Patients were identified under an institutional review board–approved chart review protocol. Patients with ALK-positive NSCLC were identified who were seen at the Stanford Cancer Center from October 1, 2007 until March 1, 2013. This cohort was generated by identifying patients with positive ALK testing from Stanford pathology after late 2010 and also by including earlier patients who were identified by ALK testing within ongoing clinical trials. Positive ALK status was determined by fluorescent in situ hybridization testing by the Food and Drug Administration (FDA) –approved test. Patients were followed from diagnosis throughout their course for treatment effect and survival through data cutoff on March 10, 2016. Retrospective chart review was performed to collect data on sex, age, race, ethnicity, Eastern Cooperative Oncology Group (ECOG) performance status, smoking history, tumor histology, stage at diagnosis, metastases at diagnosis as well as through progression,

treatment histories, date of diagnosis, and date of death. Stage was adjusted to conform to the seventh edition American Joint Committee on Cancer/International Union Against Cancer staging system (the 2009 TNM Classification of Malignant Tumors).[6]

Assessment

For assessment of therapy response, we used TOT as a real-world surrogate for radiographic progression-free survival in this cohort who were not treated or imaged in a uniform manner. This was calculated by identifying the start date as treatment initiation and specifying the end date as change in therapy, cessation of therapy, or death. This designation also allowed us to use a text-mining algorithm that could analyze solely the charts to capture treatment durations. Kaplan-Meier plots and log-rank tests were computed using the R survival package. Pearson's coefficient was computed using scikit Python package.

Database Methodology

Stanford's Cancer Research Institute has established an informatics platform (Stanford Cancer Institute Research Database) that allows for the integration of the Stanford EHR (EPIC) exports (EPIC Clarity) with many other cancer-related data sets, including the Stanford Cancer Registry, Social Security Death Index, Cancer Prevention Institute of California, Stanford Translational Research Integrated Database Environment, molecular pathology, and other data sets within Stanford. Under guidance by the Stanford Cancer Research Institute institutional review board, we are allowed to run targeted queries against the Clarity dataset for the patients with cancer within an approved study. For this particular study, we focused on queries on the basis of EPIC's Medication Order tables. Medication orders were filtered by using a case-insensitive search for orders for medications named crizotinib or Xalkori. TOT was calculated based on the difference between the minimum start date and the maximum end date for the medication order.

RESULTS

Patients

A total of 33 patients with ALK-positive NSCLC were identified. Baseline characteristics are identified in Table 1. Of note, nearly half of the patients were Asian (42%), and almost all patients were never to light smokers (88%), partially reflective of the patient population seen at our center. Eighty-five percent were diagnosed as having stage IV disease. Performance status was good at diagnosis, with the majority (80% of those with documented ECOG score) being ECOG 0 or 1. Interestingly, there were two patients who were positive for both an EGFR mutation and ALK gene rearrangement.

Treatments and Efficacy

A total of 32 patients underwent systemic treatment during the course of the study. In total, there were 70 different regimens administered to the 32 patients, of which 24 were crizotinib. Twenty-four patients who received crizotinib had a median TOT of 8.5 months (95% CI, 6.7 to 10.3). Of the 33 patients, 16 have died, with a median survival time for the deceased patients 15.5 months from diagnosis. Currently, one patient remains on crizotinib therapy and two remain on pemetrexed therapy. Five of the patients whose disease

progressed while receiving crizotinib received second-generation ALK inhibitors such as ceritinib (either on clinical trial or after FDA approval in 2014).

Automated Algorithm Results

Out of a total of 24 patients who had completed crizotinib data by the time of data cutoff (ie, had completed course of crizotinib), 15 (62.5%) were able to be automatically extracted from the Stanford EHR database (Stanford Cancer Institute Research Database; Fig 1). The reason that nine patients were unable to have results automatically extracted was primarily because crizotinib was being administered as part of a clinical trial and was therefore not entered as a medication order in the medical record (seven of nine patients). Two of the nine patients transferred care to an outside clinic. A Pearson's correlation coefficient was computed for the remaining patients (n = 15), with r = 0.39 and P = .15 (Fig 2). Examining the results, it becomes clear that there were three obvious outliers that negatively affected the correlation significantly (Fig 2; arrows in red with patient number above). These outliers were manually inspected in the EHR, and reasons for the failure of the automatic extractions are as follows. Patient 1: the drug was actually started in a clinical trial and a manually entered start date was incorrect; Patient 2: the drug end date in the medication record was entered incorrectly; Patient 3: the drug was dose reduced but accidentally marked as discontinued in the medication reconciliation. When these three outliers were excluded, the results between manual and automatic curation (n = 12) were significantly correlated with a Pearson's correlation coefficient computed at r = 0.83, with P < .001.

Outside of these outliers, the algorithmically determined EHR start date was always earlier than manually curated data (mean of 21 days earlier), and this was likely due to lag time for insurance authorization or preordering medication in anticipation of the next line of therapy. In parallel, the mined end date was generally later than the manually curated date (mean of 21 days later), which is probably due to providers discontinuing the medication using medication reconciliation in the EHR at a later date than instruction to the patient or patient self-discontinuation. As a result, the TOT of automatic curation was always longer, and this difference is appreciable in Figure 2, where all of the patient points are above the 1:1 correlation line (blue). The statistics for the absolute difference were a mean of 42 days, a median of 18 days, and a standard deviation of 56. The reason for the high mean and standard deviation are that for two patients (marked with gray arrows in Fig 2), the automated time was markedly longer than the manually curated time. One of these patients (Patient 4) had discontinued crizotinib and restarted at a later date. The other (Patient 5) had an indeterminate ALK fluorescent in situ hybridization, so preauthorization for the medication was obtained well in advance while additional biopsy testing was being obtained. Without these two outliers, the mean drops to 19.5 days, median to 12.5, and standard deviation to 12.7.

DISCUSSION

In this small pilot study, we demonstrate that an algorithm to automatically mine oncologic patient data was feasible but had some limitations that need further work. First, only 62.5% of the patients were analyzed automatically from the EHR. A large percentage of the

extraction failures were due to the nature of crizotinib being on a clinical trial for a portion of the study, thus making it inaccessible in the medication orders table. Although we expect that this problem will not arise with already-established medications, it can make studies of newly FDA-approved drugs more challenging, because there will be a period of time when medication orders are tabulated differently for the same drug. Second, there were a number of patients whose automatically extracted data were significantly inaccurate. The cause of these errors was related to provider notation error or nonstandard clinical practice pattern (eg, discontinuing drug but then restarting at a later date). Although a more diligent chart notation could ameliorate these problems, we realize that there will always be provider-based errors with which an automated algorithm relying on the medication order table will struggle. One way to bypass this would be to increase the study population and thus mitigate the effect of outliers. However, this would still be problematic for inherently small studies. A more potent method would be to develop the algorithm to use natural language processing to analyze written charts and abstract treatment information from the text. This approach is currently being worked on and will be ready for preliminary testing in the near future. Last, the automated treatment time was always longer than the manual treatment time because of issues with preauthorization and early patient-directed medication discontinuation. Aside from these two outliers, the variance seemed to be relatively consistent, and, with more data, the algorithm could potentially learn what the expected deviation is and correct for it in future studies.

One important question is whether the use of TOT as a metric rather than Response Evaluation Criteria in Solid Tumors–based progression-free survival is a valid end point for observational studies. The real-world practice patterns of continuing tolerable therapies post progression and performing imaging at less-frequent intervals makes TOT and progression-free survival not directly equivalent measures. However, recent work has indicated that improvement in time to next therapy correlates with improvement in overall survival and thus could potentially be used as a valid clinical end point.[7] This represents only a retrospective study, however, and ultimately large clinical trials will have to be examined to compare TOT to existing surrogates of outcome. With the emerging widespread use of electronic medical records, we anticipate that a validation of benefit for a given therapy will increasingly be based on data from the outcomes of large retrospective medical record searches rather than the results of individual clinical trials that include highly selected patients. Because TOT can be generated algorithmically from a medical record search, as opposed to formal radiographic progression data that require manual measurements, we expect to increasingly see large retrospective reviews use a TOT-based approach.

The potential to apply this broadly to other cohorts and other questions could be exciting. Exclusive dependence on data derived from clinical trial publications is potentially problematic, because it represents a select patient population that may not reflect general practice; the initiation of a clinical trial takes significant resources, which limits the scope of questions that can be answered; and results take a long time to mature, by which time it is possible that practice has changed. By applying bioinformatics techniques to existing and expanding EHRs, we envision the ability to more accurately assess how a patient will respond to various treatments in real time. Although this study was limited to patients with ALK NSCLC treated with crizotinib, it can be applied to other tumors and other drugs. As

more and more patients get tumor sequencing data, molecular profiles can also be incorporated, which will lead to even more nuanced and informed assessments. This may be an important aspect of the future of precision medicine trials, as demonstrated in the recent basket trial, which did not meet its primary end point potentially because results were diluted by multiple treatment groups composed of many molecular alterations spread across a modest number of patients.[8] With access to shared EHRs, the potential for large, scalable analyses will provide greater insight into molecularly off-target treatments.

In summary, we undertook a small pilot study evaluating the efficacy of an automated computational chart-mining algorithm in a select oncologic patient population (ALK-translocated NSCLC treated with crizotinib) and found that automatically abstracting TOT was feasible but had limitations that need further work. We are currently working on optimizations to the algorithm to mine text information and handle outlier cases to improve accuracy. We anticipate that this scalable methodology has the potential to eventually be used to generate meaningful conclusions that inform the treatment of patients with cancer.

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Biographies

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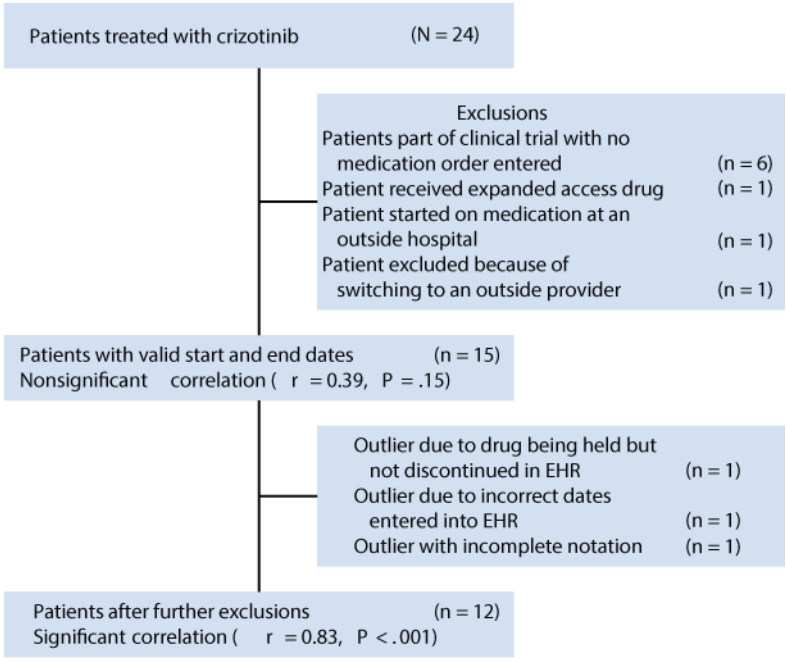

Figure 1.
Description of how patients were filtered for analysis

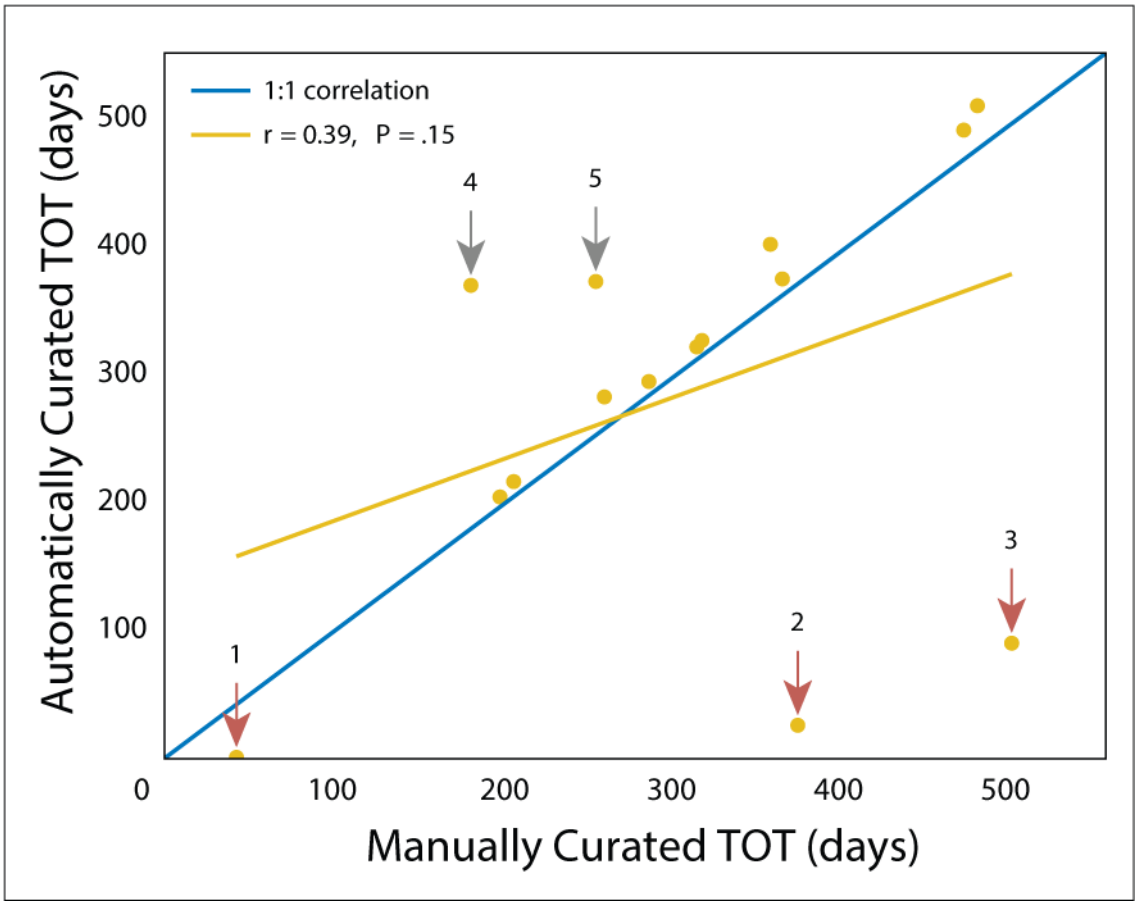

Figure 2.
Scatterplot of filtered patients' manual versus automated crizotinib time on treatment (TOT). Pearson's correlation coefficient was r = 0.39, with P = .15. A 1:1 correlation line is shown in blue. Significant outliers where the algorithm severely underestimated TOT are shown with red arrows, and overestimates are shown with gray arrows. Numbers represent patient numbers, with discussion of reasons behind outliers in the main article text.

Table 1

Patient Demographics and Clinical Characteristics

Characteristic	Measure
Age, years	
Median	53
Range	28–82
Sex	
Male	16
Female	17
Race	
White	13
Asian	14
Hispanic	4
African American	1
Smoking history	
Never smoker	21
<= 10 years	8
> 10 years	3
Stage	
IA	1
IIIA	4
IV	28
Performance status	
ECOG 0 or 1	16
ECOG 2 to 4	4

NOTE. Data presented as No. unless otherwise noted.

Abbreviation: ECOG, Eastern Cooperative Oncology Group.