Phenotyping and Visualizing Infusion-Related Reactions for Breast Cancer Patients

Deyu Sun\textsuperscript{a}, Gopal Sarda\textsuperscript{b}, Steven J. Skube\textsuperscript{c}, Anne H. Blaes\textsuperscript{d}, Saif Khairat\textsuperscript{f}, Genevieve B. Melton\textsuperscript{c,e}, and Rui Zhang\textsuperscript{c,e}

\textsuperscript{a}School of Statistics, University of Minnesota, MN, USA
\textsuperscript{b}Department of Computer Science and Engineering, University of Minnesota, MN, USA
\textsuperscript{c}Department of Surgery, University of Minnesota, MN, USA
\textsuperscript{d}Department of Medicine, University of Minnesota, MN, USA
\textsuperscript{e}Institute for Health Informatics, University of Minnesota, MN, USA
\textsuperscript{f}Carolina Health Informatics Program, University of North Carolina, NC, USA

Abstract

Infusion-related reactions (IRRs) are typical adverse events for breast cancer patients. Detecting IRRs and visualizing their occurrence associated with the drug treatment would potentially assist clinicians to improve patient safety and help researchers model IRRs and analyze their risk factors. We developed and evaluated a phenotyping algorithm to detect IRRs for breast cancer patients. We also designed a visualization prototype to render IRR patients’ medications, lab tests and vital signs over time. By comparing with the 42 randomly selected doses that are manually labeled by a domain expert, the sensitivity, positive predictive value, specificity, and negative predictive value of the algorithms are 69\%, 60\%, 79\%, and 85\%, respectively. Using the algorithm, an incidence of 6.4\% of patients and 1.8\% of doses for docetaxel, 8.7\% and 3.2\% for doxorubicin, 10.4\% and 1.2\% for paclitaxel, 16.1\% and 1.1\% for trastuzumab were identified retrospectively. The incidences estimated are consistent with related studies.

Keywords

Phenotype; Patient Safety; Algorithms

Introduction

Infusion-related reactions (IRRs) and hypersensitivity are adverse drug events (ADRs) that can occur during chemotherapy administration. Nearly all chemotherapeutic agents have the potential to induce an IRRs with various severity [1]; more frequent and severe IRRs are
labeled in black box warnings of the package inserts. Hypersensitivity is defined as an injurious immune reaction to an antigen; in this case, a component of a chemotherapy drug. An IRR is an unexpected reaction to a drug [1]. These terms are often used interchangeably in reference to adverse events, although the definition of hypersensitivity refers to an allergic reaction to a previous exposure. Here we include infusion-caused hypersensitivities as a type of IRRs. The incidence of these reactions varies widely among reports, for example, an estimate of IRRs incidence of general medications is 2–15% [2] and an estimate of IRRs incidence of trastuzumab is 0.7–40% [3]. There is lack of estimates of IRRs incidences of other medications against breast cancer. The signs and symptoms of these adverse events are broad, often difficult to define, and include all organ systems. Examples include anaphylaxis, rash, respiratory distress, hypotension, nausea, flushing, and fatigue. The severity of these reactions is mild to severe, in rare instances leading to death [1].

Currently, the detection of IRRs is based on manual chart review [3–5]. An appropriate phenotyping algorithm not only would assist clinicians increase performance to detect IRRs, avoid information overload, and ultimately improve patient safety, but also benefit researchers in modeling and analyzing risk factors of IRRs.

Moreover, in the highly time constrained clinical care setting, visualizing patients’ active medication status and associated IRRs may assist clinicians in avoiding medication errors and would also assist researchers in understanding clinical correlations. Most current visualization systems focus on showing structured data alone, without integrating additional knowledge and phenotyping algorithms, such as serious ADRs associated with medication usage. In this pilot study, we developed and evaluated a phenotyping algorithm for identifying IRRs with four first-line breast cancer drugs, namely, docetaxel, doxorubicin, paclitaxel, and trastuzumab. In addition, we further developed a visualization prototype for correlating associated IRRs with the drugs for individual patients.

**Methods**

As illustrated in Figure 1, the methods consist of four parts: (1) extracting IRRs from structured drug product labels; (2) collecting relevant EHR data; (3) detecting IRRs by the designed phenotyping algorithm; and (4) rendering IRRs detected by visualization prototype and evaluation.

In this study, we focus on the 63 brands of medications with 28 different chemical makeups approved by Food and Drug Administration (FDA) to treat breast cancer [6]. Using a previously described approach, we first extracted all IRRs (including infusion-caused hypersensitivities) from the current package inserts, i.e., FDA Structured Product Labels (FDA SPL) annotated by natural language processing (NLP) algorithms [12]. Five medications (i.e., docetaxel, doxorubicin, epirubicin, paclitaxel, and trastuzumab) among these have black box warnings of IRRs (including infusion-caused hypersensitivities) [7–11]. Since epirubicin is not found in our patient cohort, we only focus on other four medications in this study.
Clinical data for breast cancer patient cohort stored in the Fairview Epic EHR were extracted from the University of Minnesota clinical data repository. Using the domain knowledge, we categorized the IRRs into 17 symptoms according to their similarity in medicine (Table 1) and listed all the related ICD-9-CM and ICD-10-CM codes, which would be used in our phenotyping algorithm (Figure 2).

As shown in Table 1, the symptoms of the IRRs are quite broad, e.g., from chills to nausea, from hypotension to fatigue. To include comprehensive information from EHR data, we used various heterogeneous data (e.g., diagnosis, lab results, and clinical notes) for IRRs detection. Collaborating with clinical experts from University of Minnesota Medical Center (UMMC), we developed a phenotyping algorithm using related concepts mentioned in the unstructured clinical notes, dynamic changes of lab tests from baseline, and related diagnosis codes (Figure 2).

Clinical notes were found containing important indicators of IRRs during the retrospective chart review by clinicians. We used open-source natural language processing (NLP) tool, BioMedICUS (BioMedical Information Collection and Understanding System) [13], to search related biomedical concepts in patients’ clinical notes. BioMedICUS is an open-source NLP system based on the Unstructured Information Management Architecture – Asynchronous Scaleout (UIMAAS) architecture specialized in NLP-related information extraction and understanding of clinical notes. BioMedICUS identifies UMLS Metathesaurus concepts (concept unique identifiers, or CUIs) from lexical variants expressed in the notes, and whether the identified concepts were used in a negated context. As shown in Table 2, we include CUIs related to the synonyms of IRRs (Table 2) within the 24 hours of infusions of docetaxel, doxorubicin, paclitaxel, or trastuzumab from patients’ clinical notes as inputs illustrated in our phenotyping algorithms (Figure 2).

In addition to clinical notes, patients with IRRs usually show abnormal lab test values, vitals, or diagnoses of abnormal syndromes. However, as shown in table 1, such syndromes are not specific to IRRs. To precisely attribute reactions to infusions, we not only apply temporal constraints (i.e. abnormal syndromes should happen within 12 hours of infusions), but also consider the change from baseline (i.e. only the syndromes that break out after infusion but not exist one month before infusion (baseline) are viewed as evidence of IRRs). The baseline of lab tests and vitals is defined as the most recent measurement within one month before infusion. The abnormal change from baseline within 12 hours can be found in two scenarios.

- First, the qualitative change, a change from a negative state at baseline to positive after infusion, e.g., a type of syndrome (diagnosed by ICD-9-CM or ICD-10-CM) shown in Table 1 that did not exist within one month before infusion but broke out right after infusion. Similar cases include WBC changes from normal (≤11×10%/L) at baseline to abnormally high after infusion (>11×10%/L), lactic acid changes from normal (≤2.0mmol/L) to abnormally high (>2.0mmol/L), and oxygen saturation changes from normal (≥90) to abnormally low (<90).

- Secondly, quantitative change, a sufficiently large change in measurements from the baseline, e.g. the blood pressure in Mean Arterial Pressure (MAP = [(2 x diastolic) + systolic] divided by 3) with a change of no less than 10 mmHg, or a
change in temperature of more than 2 Fahrenheit, or a change in respiration rate of more than 5, or a change in heart rate of more than 20 beats/min.

Only the abnormal syndromes meeting both the temporal constraints and the requirement of sufficient changes from baseline serve as evidence of IRRs. For evaluation, 42 doses of the four medications were randomly selected, the clinician then manually reviewed the charts and labeled each case as true IRR (13 cases) or false IRR (29 cases). The detection results of the phenotyping were then compared with the expert curated gold standard. The sensitivity, positive predictive value (PPV), specificity and negative predictive value (NPV) were reported. We also compared the incidence rates of IRRs on patients who used these four medications in our EHR data.

We have also created a visualization prototype to render the entire medications, vitals, labs and diagnosis data for a patient over time by using Grails framework. The interface of the visualization tool is shown and detailed in the Results section. We randomly selected two patients with true positive IRRs detected by our phenotyping algorithms and visualized their breast cancer medications and any related lab values and symptoms existed in Fairview EHR data.

Results

We applied our phenotyping algorithms into the cohort consisting of 4,084 breast cancer patients treated from the fourth quarter of 2000 to the second quarter of 2016. There are total 236,069 doses of all medications. Table 3 shows the total patients and doses of docetaxel, doxorubicin, paclitaxel, and trastuzumab. Note, epirubicin is not used in UMMC.

As an evaluation, a clinician from UMMC manually diagnosed 42 doses by chart review. Table 4 shows the detection results by our phenotyping algorithms. The sensitivity and PPV of the algorithm are 69% and 60%, respectively, while the specificity and NPV are 79% and 85%, respectively.

As shown in Table 5, the prevalence of IRRs in patients who get infusions of docetaxel, doxorubicin, paclitaxel, and trastuzumab are 6.4%, 8.7%, 10.4%, and 16.1%, respectively, while the IRRs rates of all doses of docetaxel, doxorubicin, paclitaxel, and trastuzumab are 1.8%, 3.2%, 1.2, and 1.1%, respectively.

Figure 3 renders two IRRs events. The visualization supports viewing two types of data at a time. The time axes for all the types of data are aligned. With medication information always displayed, clinicians can select one of the Vitals/Labs/Diagnosis panel as the other data source. Each medication consumption information is represented by a horizontal bar, with length of the bar reflecting the duration of consumption and height of the bar reflecting the dosage of the medicine. Since, there can be many interesting vitals/labs corresponding to a patient, the visualization provides an option to select one of the many vitals/labs available. Normal ranges for a lab/vital are also marked using the red and blue dotted lines as can be seen in Figure 3. The diagnosis data is displayed in a grid format with rows as different type of diagnosis and columns as time. A dot in a cell indicates a type of diagnosis reported on the date. The IRRs in Figure 3(a) was detected by abnormal change in blood pressure from
the baseline. We can see the baseline blood pressure is 75.67mmHg measured at 9:50 am; after the patient gets infusion at 4:24 pm (labeled by the blue bar inside the block denoting a paclitaxel infusion), the blood pressure increases by 11.66mmHg, up to 87.33mmHg, which indicates an IRRs. Figure 3(b) shows another IRRs detected by the breaking-out of a syndrome. We can see after getting infusion at 12:49 pm on 3/12/2012, the patient experienced chills and nausea on 3/13/2012; considering the clinical note of the patient also mentions the IRRs, the phenotyping algorithm classifies the reactions as IRRs.

Discussion

The incidences of the IRRs detected by our phenotyping algorithm are consistent with other researchers’ studies. The incidence of four medications (docetaxel, doxorubicin, paclitaxel, and trastuzumab) varies from 6.4% to 16.1% of patients, which is consistent with the results reported (a wilder estimate, 0.7%–40% [2], and a more precise estimate 2–15% [3]). By manual chart review, L. M. Thompson et al detected 33 patients with 33 IRRs out of 197 patients with 1,788 doses of trastuzumab, resulting in an incidence of 16.2% of patients and 1.8% of doses; our method has quite close incidence to these results (16.1% of patients and 1.1% of doses).

Developing phenotyping algorithm to detect IRRs is vital for patient safety. Compared to the manual review in time-constrained clinical setting, automatic detection would greatly improve the performance of clinicians in finding ADRs. Accessing various types of EHR data for patients in a short time would potentially aid clinicians in making decision or changing treatment plans.

According to evaluation results, our phenotyping method has a better performance of classifying negative cases (with specificity of 79% and NPV of 85%), indicating it would be useful in reducing clinicians’ workload by filtering out negative doses. On the other hand, we analyzed the relatively high false positive cases and found that most of the false positive cases are detected by changes in diagnoses (i.e. ICD codes), which is due to inaccurate time of diagnoses. The time of diagnosis recorded in the EHR database is usually one day delayed after the syndrome actually broke out (since coding takes time), as a result, some IRRs caused by previous doses were falsely identified to be caused by later doses.

Our pilot work is limited by the collection of gold standard. Since chart review is time-consuming and expensive, we only have a small size of labeled cases (42 for now) created by one physician, which limits the precision of our evaluation. Currently, the parameters of the phenotyping method are estimated based on expert’s domain knowledge without referring to guidelines. In future, we are going to collaborate with more domain experts and incorporate more information, such as allergy history, and more knowledge, such as the guidelines, to automatically generate more labeled cases and improve parameter estimations by using data-driven methods.

Conclusion

In this study, we proposed a phenotyping algorithm to detect IRRs for breast cancer patients who took docetaxel, doxorubicin, paclitaxel, and trastuzumab. The phenotyping algorithm
was evaluated by expert chart review. The sensitivity, PPV, specificity, and NPV are 69%, 60%, 79%, and 85%, respectively. We also developed a visualization prototype, which integrates and visualizes multiple information such as medications, vital signs, and lab test results over a specific period in one interface. The phenotyping algorithm and visualizing prototype developed in the study have potential to be adapted to detect IRRs caused by other medications. Such phenotyping algorithm and visualization method can also be applied to the clinical decision support system to improve the healthcare efficiency and patient safety.

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Figure 1.
Flowchart of the method

Extracting IRRs from package insert

Collecting cohort data from EHR

Detecting IRRs by phenotyping algo-

Evaluating and Visualizing results
Figure 2.
IRRs phenotyping algorithm
Figure 3.
Visualization of two IRRs events (a) An IRR detected by greatly increased blood pressure after the infusion of 141 mg of paclitaxel. (b) An IRR of chills and nausea after the infusion of 140 mg of docetaxel.
Table 1
Categories of IRRs Associated with docetaxel, doxorubicin, paclitaxel, and trastuzumab

| Group Names | ICD9CM | ICM10CM |
|-------------|--------|---------|
| Angioedema  | 277.6  | D84.1   |
| Headache    | 339.3, 784.0 | G44.41, G44.1, R51 |
| Hypertension| 405    | I15.0, I15.8 |
| Tachycardia | 427.0, 427.1, 427.2, 785.0 | I47.1, I47.2, I47.9, R00.0 |
| Hypotension | 458    | I95.1, I95.89, I95.3, I95.2, I95.81, I95.9 |
| Cough       | 519.11, 786.0, 786.2, 786.5, 786.9 | I98.01, R06.9, R06.4, R06.01, R06.81, R06.3, R06.02, R06.82, R06.2, R06.00, R06.09, R06.83, R06.89, R07.9, R07.2, R07.1, R07.81, R07.82, R07.89, R05 |
| Erythema    | 695    | L53.0, L53.1, L53.2, L51, L52, L71.0, L71.1, L71.8, L93.0, L93.2, L49.0, L49.1, L49.2, L49.3, L49.4, L49.5, L49.6, L49.7, L49.8, L49.9, L00, L26, L30.4, L53.8, L92.0, L95.1, L98.2, L53.9 |
| Pruritus     | 698.8, 698.9, 708 | L29.8, L29.9, L50.0, L50.1, L50.2, L50.3, L50.4, L50.5, L50.6, L50.8, L50.9 |
| Pain         | 719.4, 724.5, 724.8, 724.9 | M25.50, M25.519, M25.529, M25.539, M25.549, M25.569, M25.579, M54.89, M54.9, M54.08, M43.8X9, M53.9 |
| Fibromyositis| 729.1  | M60.9, M79.1, M79.7 |
| Chills       | 780.64 | R68.83 |
| Fatigue      | 780.79 | G93.3, R53.1, R53.81, R53.83 |
| Dizziness    | 780.4  | R42 |
| Hyperhidrosis| 780.8  | R61 |
| Flushing     | 782.62, 782.1 | R23.2, R21 |
| Nausea       | 787.02, 787.01, 787.03 | R11.0, R11.2, R11.10, R11.11, R11.12 |
| Miscellaneous| 780.99, 995.0, 995.1, 995.2, 995.3, 995.9 | A41.9, R45.84, R65.10, R65.11, R65.20, R65.89, T50.905A, T36.*X5A, T37.*X5A, T38.*X5A, T38.8*5A, T38.9*5A, T39.0*5A, T39.*X5A, T39.3*5A, T39.9*5A, T40.*X5A, T40.0*5A, T40.9*5A, T41, T42.*X5A, T42.75XA, T43.0*5A, T43.*X5A, T43.2*5A, T43.5*5A, T43.6*5A, T43.9*5A, T44.*X5A, T44.9*5A, T45.*X5A, T45.5*5A, T45.6*5A, T45.9*5A, T46.*X5A, T46.9*5A, T47.*X5A, T47.9*5A, T48.*X5A, T48.2*5A, T48.9*5A, T49.*X5A, T50.*X5A, T50.9*5A, T50.*A*5A, T50.B*5A, T50.Z*5A, T78.3*XA, T78.2*XA, T78.4*XA, T88.52XA, T88.59XA |
Table 2
Categories of IRRs Associated with doceael, doxorubicin, paclitaxel, and trastuzumab

| Group Names    | UMLS CUI                                      |
|----------------|----------------------------------------------|
| Angioedema     | C0002994, C0038999                           |
| Headache       | C0018681                                     |
| Hypertension   | C1963138                                     |
| Tachycardia    | C0039231                                     |
| Hypotension    | C0020649, C3163620                           |
| Cough          | C0010200, C0006266, C0008031, C0013404, C0232292, C0236071 |
| Pruritus       | C0033774                                     |
| Pain           | C0003862, C0004604, C1963071                 |
| Fibromyositis  | C0231528                                     |
| Chills         | C0085593, C0026837                           |
| Fatigue        | C0015672, C0023380, C0231218                 |
| Dizziness      | C0012833                                     |
| Hyperhidrosis  | C0700590                                     |
| Flushing       | C0016382, C1962957, C0015230, C0221232       |
| Nausea         | C0027497, C0042963                           |
| Miscellaneous  | C0020517, C0002792, C0750016, C0020538, C0042109, C0020538 |
Table 3

Number of patients and doses on docetaxel, doxorubicin, paclitaxel, and trastuzumab in UMMC

|             | # of Patients | # of doses |
|-------------|---------------|------------|
| docetaxel   | 188           | 857        |
| doxorubicin | 435           | 1,676      |
| paclitaxel  | 576           | 5,918      |
| trastuzumab | 323           | 6,741      |
Table 4

Patients and doses taking docetaxel, doxorubicin, paclitaxel, and trastuzumab in UMMC

|        | True IRRS | False IRRS |
|--------|-----------|------------|
| Positive | 9         | 6          |
| Negative | 4         | 23         |
|               | % of Patients | % of Doses |
|---------------|---------------|------------|
| docetaxel     | 6.4           | 1.8        |
| doxorubicin   | 8.7           | 3.2        |
| paclitaxel    | 10.4          | 1.2        |
| trastuzumab   | 16.1          | 1.1        |

Table 5
IRRs rate among patients taking docetaxel, doxorubicin, paclitaxel, and trastuzumab in UMMC