Preliminary Development and Evaluation of an Algorithm to Identify Breast Cancer Chemotherapy Toxicities Using Electronic Medical Records and Administrative Data

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Abstract

Purpose: Breast cancer chemotherapy toxicity is not well documented outside of randomized trials. We developed and conducted preliminary evaluation of an algorithm to detect grade 3 and 4 toxicities using electronic data from a large integrated managed care organization.

Methods: The algorithm used administrative, pharmacy, and electronic data from outpatient, emergency room, and inpatient records of 99 women diagnosed with breast cancer from 2006 to 2009 who underwent chemotherapy. Data were abstracted for 12 months post-treatment initiation (24 months for trastuzumab recipients). An oncology nurse independently blindly reviewed records; these results were the “gold standard.” Sensitivity and specificity were calculated for overall toxicity, categories of toxicities, and toxicity by age or regimen. The algorithm was applied to an independent sample of 1,575 patients with

breast cancer diagnosed during the study period to estimate prevalence rates.

Results: The overall sensitivity for detecting chemotherapy-related toxicity was 89% (95% CI, 77% to 95%). The highest sensitivity was for identification of hematologic toxicities (97%; 95% CI, 84% to 99%). There were good sensitivities for infectious toxicity, but rates dropped for GI and neurological toxicities. Specificity was high within each category (89% to 99%), but when combined to measure any toxicity, it was lower (70%; 95% CI, 57% to 81%). When applied to an independent chemotherapy sample, the algorithm estimates a 26% rate of hematologic toxicity; rates were higher among patients age ≥ 65 years versus less than 65 years.

Conclusions: If validated in other samples and health care settings, algorithms to capture toxicity could be useful in comparative and cost-effectiveness evaluations of community practice–delivered treatment.

Introduction

Advances in cancer chemotherapy have been credited with reductions in mortality.^{1,2} However, this progress has been accompanied by greater risks of toxicity.³⁻⁶ Assessment of treatment toxicity is straightforward in most randomized clinical trials, given prospective toxicity reporting. However, the majority of the population receives their care outside of research settings,^{7,8} where comparing outcomes of different regimens in varying patient subgroups depends on the availability of data from medical records to retrospectively identify toxicity. Toxicity data are also important to our understanding of population-level economic outcomes, because toxicity events can be costly⁸ and could affect conclusions about cost effectiveness of treatment regimens, including personalized approaches.⁹⁻¹³

Unfortunately, despite the considerable investment in developing electronic medical records,¹⁴ and the large proportion of oncology encounters in those records, there is currently no efficient, validated method to routinely identify the toxicity of chemotherapy regimens from these systems. In research settings, prior studies have attempted to manually review records or analyze insurance claims to identify conditions likely to in-

volve toxicity.^{8,15-18} These types of data have been used to construct adverse event rates and examine factors associated with risk or costs of adverse treatment effects.^{8,16,19} However, none of these studies evaluated the accuracy of their methods for capturing toxicity events, and they represent labor-intensive and costly approaches. To investigate the feasibility of non-manual methods, one study compared clinical trial data to Medicare claims and found that toxicities were not well captured in claims.²⁰

In this article, we present data on the development and preliminary performance of an algorithm to retrospectively identify chemotherapy-related toxicities from electronic medical record and administrative data for women with breast cancer treated in a large, integrated managed care organization. We focus on conditions and events associated with National Cancer Institute (NCI) Common Toxicity Criteria grade 3 and 4 events,²¹ since these are most likely to be important in treatment, formulary, and coverage decisions. When validated in independent samples, the algorithm could support future research to identify subgroups of women most likely to benefit from systemic therapy at the lowest risk (and least costs).

Methods

This study was conducted at Kaiser Permanente of Northern California (KPNC) in collaboration with Georgetown University and Columbia University. The protocol was approved by institutional review boards at all collaborating institutions. Kaiser maintains its medical records in an electronic format. All cancer cases are linkable to the population tumor registry.²² Administrative and noninfusion pharmacy data are also available in an electronic format.²³ There is a high membership retention rate after cancer diagnosis, and data are available for care received outside of Kaiser, making this an ideal setting for this investigation.²⁴

Population

We identified all patients 21 years or older who were diagnosed from 2006 to 2009 with primary invasive, nonmetastatic breast cancer. Chemotherapy use was defined on the basis of pharmacy records for the common regimens. An age-stratified (younger than 65 years *v* 65 years and older), block random sample was drawn from the women who received chemotherapy. We oversampled older women because they were expected to have higher toxicity rates than younger women.²⁵ The analytic sample included 99 women who received chemotherapy. This was deemed to be a feasible size for algorithm development. The algorithm was applied to an independent sample of women who received chemotherapy (*N* = 1,575) to estimate rates of toxicity.

Algorithm Development

We focused on events listed in the NCI Common Toxicity Criteria as grade 3 or 4 chemotherapy-related toxicities²¹ because they were deemed relevant to patient outcomes. Grade 1 and 2 toxicities, such as fatigue and nausea, were excluded as they represent mild and moderate and more transient symptoms that are not generally well captured in health records.

We then enumerated an inclusive list of conditions, diagnoses, laboratory results, procedures, and medications that might be related to grade 3 or 4 toxicity events associated with breast cancer chemotherapy regimens. We identified all possible codes associated with these events. The list was reviewed by study oncologists (D.H.L., C.I.) to ensure that all relevant events were included. Examples of events or diagnoses included hospitalization for febrile neutropenia, having an absolute neutrophil count less than 1,000, or diarrhea and dehydration requiring hospitalization or intravenous hydration. The conditions were chosen for their face validity for being related to chemotherapy (*v* radiation or hormonal therapy, each of which has different adverse event profiles from acute chemotherapy toxicity).

We considered conditions from the start date of chemotherapy to 12 months after treatment initiation; for trastuzumab, we considered events occurring up to 24 months after start of first chemotherapy. We restricted our definition of toxicity to conditions that were not present or only occurred rarely in the 6 months before cancer diagnosis. Conditions that occurred in less than 5% of the sample (eg, delirium) were excluded from the final algorithm.

Because agents such as filgrastim, erythropoietin or darbepoietin are used for both prevention of hematologic toxicity and treatment of established toxicity, we considered only the administration of these agents with a preceding or concurrent diagnosis indicating marrow suppression (eg, neutropenia, anemia, blood transfusion) as a potential adverse toxicity event. Conditions such as diarrhea or fever were coded as toxicity if they were noted on more than one encounter during chemotherapy or were accompanied by concurrent codes for hospitalization, intravenous hydration, or infection.

Similar to the iterative method defined by Lamont et al,²⁰ we refined the algorithm to remove codes that were not specific enough to chemotherapy. Trained medical record abstractors confirmed information on toxicities for coding quality assurance purposes. The conditions and codes included in the final algorithm are described in Appendix Table A1 (online only).

Data Collection

The algorithm was used to abstract data from administrative, pharmacy, and electronic data from outpatient oncology and nononcology, emergency room, and inpatient medical record systems. We attempted to use text fields for chief complaints but found that the text was too nonspecific to attribute to chemotherapy toxicity and/or to ascertain toxicity grade (eg, text notes of “nausea” or “vomiting”).

An oncology nurse independently reviewed the sample to determine whether the patient had experienced a toxicity related to chemotherapy using the NCI Common Toxicity Criteria. The oncology nurse review was considered the “gold standard” because she could interpret constellations of events or observe clinical notations of toxicity that might not be captured by the electronic algorithm. The nurse was blind to the algorithm’s classification of toxicity. After the review was complete, we examined discordant results to identify any coding errors. For instance, when calculating the absolute neutrophil count from the algorithm, if the code was correct, the results should always agree with those calculated by the nurse from the same laboratory results on the same dates.

Statistical Analysis

The primary definition of toxicity using the algorithm was having any toxicity (*v* none). We also examined individual classes of toxicity and a definition of toxicity restricted to the most prevalent and potentially life-threatening conditions, including hematologic, infectious, and diarrhea/dehydration toxicities. We estimated overall and age-stratified sensitivities and specificities (and corresponding 95% CIs) of the algorithm, using the assessment of the oncology nurse as the gold standard. Sensitivity was defined as the number of cases correctly identified as having toxicity by the algorithm divided by all cases identified by the gold standard as having toxicity. Specificity was defined as the number of cases correctly identified as not having toxicity by the algorithm divided by all cases identified by the gold standard as not having toxicity. CIs were calculated using the Wilson (Score) method for confidence limits for a binomial proportion. Because we oversampled older women and drew a

block sample of women who had undergone chemotherapy, we were not able to calculate the positive and negative predictive values for the algorithm. We further explored whether the algorithm performance varied by type of toxicity, age group (younger than 65 years *v* 65 years and older), or class of regimen (anthracycline *v* nonanthracycline).

We then applied the algorithm to an independent sample reported to the KPNC Cancer Registry during the study period (2006-2009) who received chemotherapy (and enrolled in the Pathways study of cancer survivorship)²⁴ to calculate estimated toxicity rates (and 95% CIs around the point estimates) that could be compared with published rates from clinical trials and other studies as a measure of face and construct validity of the algorithm. Finally, we applied the algorithm to women from the same population diagnosed during the study period who did not have chemotherapy to determine “false positive” rates. Analyses were conducted using SAS v. 9.3.

Results

The women included in the development of the toxicity algorithm were primarily white (84.5%), and the majority had stages beyond stage 1 invasive cancer. The predominant regimens were anthracycline based (75%); 68% received taxanes and 27% received trastuzumab.

The highest sensitivity (97%; 95% CI, 84% to 99%) was for identification of hematologic toxicities (Table 1). There were good sensitivities for infectious toxicity, but rates dropped for GI and neurological adverse events. There were wide CI for several toxicity categories as a result of the small number of events.

The overall sensitivity of the algorithm for detecting any chemotherapy-related toxicity was 89% (95% CI, 77% to 95%) and was slightly higher among the three most prevalent classes of toxicity (Table 1). Within each category of toxicity, there are few false positive results, but when combined to measure any toxicity event, the overall algorithm specificity is 70% (95% CI, 57% to 81%). When the algorithm was applied to a sample of 250 patients with breast cancer who did not receive chemotherapy, 20% were falsely classified by the algorithm as having chemotherapy-related toxicity, consistent with the specificity results.

Sensitivity tended to be slightly higher for women 65 years or older versus those younger than 65, but generally the CIs overlapped for the two age strata (Table 1). Because 76% of women received anthracyclines, and there were higher toxicity rates associated with anthracycline versus nonanthracycline regimens (61% *v* 42%), the algorithm's sensitivity tended to be higher for anthracycline-based versus other regimens (94% [95% CI, 82% to 98%] *v* 67%; [95% CI, 35% to 88%]), but specificity was similar by regimen (data not shown).

Finally, applying the algorithm to an independent sample (Table 2), the rates of toxicity among those who received chemotherapy ranged from 1% for nephrotoxicity and 6% for Cardiotoxicity to 42% for any hematologic toxicity (Table 3). Toxicity rates were similar by age, except for higher rates of Cardiotoxicity among those 65 and older compared with those

younger than 65 (12% *v* 5%). As expected on the basis of the moderate specificity, there was a 15% to 31% toxicity rate among women not receiving chemotherapy, depending on age group (not shown).

Discussion

This is the first study that we are aware of to develop and apply an algorithm based on electronic data to estimate the rates of breast cancer chemotherapy toxicity in a large community managed care setting with full electronic data capture. The results indicate that the overall sensitivity for detecting any toxicity during active therapy is high as the most prevalent events (eg, hematologic toxicity) are readily captured from laboratory data available in records. The specificity is good for most individual classes of toxicity but is lower for any toxicity. There were no meaningful differences in algorithm performance by age group or type of systemic therapy regimen. Applying the preliminary algorithm to an independent sample in this community setting suggests that there may be a high rate of grades 3 and 4 toxicities associated with chemotherapy during the active treatment phase.

The test performance we observed using all available electronic data is substantially greater than that reported by Lamont et al using Medicare claims.²⁰ For instance, they noted ranges of sensitivities for detection of hematologic toxicities among patients with lung and breast cancer treated on clinical trials of 45% to 86%, with a median of 63%, whereas we had a sensitivity of 97% for this category. The improved performance of our algorithm is likely attributable to the fact that our access to laboratory data allowed capture of specific objective laboratory results corresponding to the Common Toxicity Criteria definitions, whereas Medicare claims do not include these data.^{20,26} Our range of specificity values is comparable to that noted in Lamont's study.

As with any test, the optimal balance between sensitivity and specificity depends on its intended uses and the impact of missing true positives versus falsely labeling an individual as positive. We developed this algorithm to have maximal sensitivity, so that all possible toxic adverse events could be captured for research on comparative and cost effectiveness of cancer chemotherapy outside of trial settings. Consequently, the codes included were broad and resulted in some instances of false-positive classification. However, we felt it was desirable to overestimate rather than underestimate toxicity in a comparative effectiveness setting. Also, some events defined as chemotherapy toxicity can occur in the postsurgical period even in the absence of chemotherapy (eg, fever, infection), therefore lowering specificity.

The rates of grades 3 and 4 toxicities estimated by our algorithm among the independent sample of patients with breast cancer are comparable to those reported directly from clinical trials^{6,27,28} and prior observational studies.²⁹ For instance, Muss reported 60% to 70% rates of grades 3 and 4 hematologic toxicities among older women enrolled onto the standard treatment arm of a chemotherapy trial, similar to our rate of 65% in this age group using similar regimens.^{3,6,27} Among patients

Table 1. Sensitivity and Specificity of an Algorithm to Measure Toxicity of Breast Cancer Chemotherapy During Active Treatment* Based on Electronic Health Data From an Integrated Health Care System

Toxicity	Denominator	With Toxicity		Sensitivity		Specificity	
		No.	%	%	95% CI (%)	%	95% CI (%)
Hematologic							
All	99	35	35	97	84 to 99	94	86 to 98
< 65 years old	50	14	28	92	65 to 99	92	79 to 97
≥ 65 years old	49	21	43	100	84 to 100	97	83 to 99
GI (diarrhea, dehydration)							
All	99	16	16	60	31 to 83	89	81 to 94
< 65	50	10	20	100	44 to 100	85	72 to 93
≥ 65	49	6	12	43	16 to 75	93	81 to 98
Infectious							
All	99	13	13	73	43 to 90	94	87 to 98
< 65	50	5	10	80	38 to 96	98	88 to 100
≥ 65	49	8	16	67	30 to 90	91	78 to 96
Cardiac							
All	99	10	10	60	23 to 88	93	85 to 96
< 65	50	3	6	67	21 to 94	98	89 to 100
≥ 65	49	7	14	50	9 to 91	87	75 to 94
Neuropathy							
All	99	6	6	33	10 to 70	96	89 to 98
< 65	50	1	2	0	0 to 0	98	89 to 100
≥ 65	49	5	10	50	15 to 85	93	82 to 98
Mucositis							
All	99	2	2	0	0 to 0	98	93 to 99
< 65	50	1	2	0	0 to 0	98	90 to 100
≥ 65	49	1	2	0	0 to 0	98	89 to 100
Nephrotoxicity							
All	99	3	3	100	34 to 100	99	94 to 100
< 65	50	0	0	0	0 to 0	100	93 to 100
≥ 65	49	3	6	100	34 to 100	98	89 to 100
Hematologic/infectious/GI							
All	99	48	48	92	80 to 97	80	68 to 88
< 65	50	20	40	87	62 to 96	80	64 to 90
≥ 65	49	28	57	96	80 to 99	80	61 to 91
Any toxicity							
All	99	56	56	89	77 to 95†	70	57 to 81†
< 65	50	22	44	78	55 to 91	75	58 to 87
≥ 65	49	34	69	96	82 to 99	64	43 to 80

* Active treatment is defined as the period from start of chemotherapy plus 12 months (or 24 months for those receiving Herceptin).

† These values correspond to an area under the curve of 0.8 for a binary test.

with breast cancer of all ages in a clinical trial of anthracycline and taxane regimens, Citron et al reported grades 3 and 4 hematologic toxicity rates of 24% to 43%³⁰; the upper range is similar to our rate of 42%. The most prevalent events detected by our algorithm were hematologic; these are the most commonly recorded events in breast cancer clinical trials for comparable regimens.²⁸ Similar to studies using SEER, SEER-Medicare, and/or other data,^{6,29,31,32} we noted a tendency for higher rates of toxicity among patients 65 and older compared with younger patients and a trend for differing toxicity profiles by regimen, supporting the face validity of our algorithm.

However, despite access to full capture of all electronic patient data in a large, integrated managed care setting with long-standing data systems, our algorithm did not have perfect performance. One explanation is that transient acute toxicities are incompletely recorded in text fields or not coded by providers,³³ limiting the ability of electronic algorithms to adequately capture these events. For instance, we found that text fields for chief complaints were not sufficiently detailed to determine whether events like nausea or diarrhea were attributable to chemotherapy or were of sufficient severity to be rated as grade 3 or 4 events. Overall, our results suggest that the feasibility of using

Table 2. Characteristics of Patients With Breast Cancer in the Independent Sample From the Target Population* From an Integrated Health Care System Who Received Chemotherapy in 2006-2009

Characteristic	Age at Diagnosis (years)					
	Overall		< 65		≥ 65	
	No.	%	No.	%	No.	%
Total	1,575	100	1,277	100	298	100
Age, years						
< 54	779	49	779	61	N/A	N/A
55-64	498	32	498	39	N/A	N/A
65-74	250	16	N/A	N/A	250	84
≥ 75	48	3	N/A	N/A	48	16
Race						
Asian	218	14	204	16	14	5
Black	137	9	118	9	19	6
White	1,075	68	826	65	249	84
Other	145	9	129	10	16	5
Hispanic†						
No	1,369	87	1,097	86	272	91
Yes	204	13	178	14	26	9
AJCC6 stage‡						
1	470	30	392	31	78	26
2a/2b	771	49	620	49	151	51
3a/3b/3c/	319	20	252	20	67	22
Anthracyclines						
No	476	30	340	27	136	46
Yes	1,099	70	937	73	162	54
Taxanes						
No	530	34	404	32	126	42
Yes	1,045	66	873	68	172	58
Trastuzumab						
No	1,251	79	1,010	79	241	81
Yes	324	21	267	21	57	19

Abbreviations: AJCC, American Joint Committee on Cancer; N/A, not applicable.

* Study population from Kwan et al.²⁴

† Two patients with unknown ethnicity.

‡ Fifteen patients with unknown stage.

electronic oncology medical records to record toxicities in community settings could be enhanced by inclusion of explicit preformatted fields specifying type and grade of toxicity, rather than relying on natural language processing. This would allow clinicians to easily enter toxicity-related adverse events, including the classification and severity grade, and would enable evaluation and comparison of different therapeutic approaches to cancer care for practice improvement and research purposes.

There are several limitations that need to be considered in evaluating our findings. First, and foremost, the algorithm was developed from a small training sample and has not yet been validated in an independent data set. Although the preliminary algorithm predicts rates of events similar to those observed in clinical trials, it will be important to validate our approach in new datasets, including those with larger sample sizes (to in-

Table 3. Application of Electronic Record–Based Algorithm to the Independent Sample of Patients With Breast Cancer From the Target Population*: Overall and Age-Stratified Prevalence of Grades 3 and 4 Chemotherapy-Related Toxicities During Active Treatment†

	Age at Diagnosis (years)					
	Overall Sample		< 65		≥ 65	
	No.	%	No.	%	No.	%
Totals	1,575	100	1,276	100	299	100
Hematologic toxicity	910	58	746	58	164	55
No						
Yes	665	42	530	42	135	45
GI (diarrhea and dehydration)	1,375	87	1,123	88	252	84
No						
Yes	200	13	153	12	47	16
Infectious and febrile	1,319	84	1,066	84	253	85
No						
Yes	256	16	210	16	46	15
Cardiac	1,474	94	1,212	95	262	88
No						
Yes	101	6	64	5	37	12
Neuropathy	1,196	76	964	76	232	78
No						
Yes	379	24	312	24	67	22
Mucositis	1,515	96	1,224	96	291	97
No						
Yes	60	4	52	4	8	3
Nephrotoxicity	1,561	99	1,269	99	292	98
No						
Yes	14	1	7	1	7	2
Subgroup of hematologic/infectious/GI	785	50	641	50	144	48
No						
Yes	790	50	635	50	155	52
Any toxicity	587	37	483	38	104	35
No						
Yes	988	63	793	62	195	65

* Study population from Kwan et al.²⁴

† Active treatment is defined as the period from start of chemotherapy plus 12 months (or 24 months for those receiving Herceptin).

crease precision for uncommon events) and from different health care systems. It is possible that this approach will not be feasible in settings without robust electronic records or in situations where patients receive care in multiple, nonintegrated systems. At present, the rate of false positive toxicity events also means that its use will overestimate true treatment toxicity. It will be important to validate the algorithm and consider the direction of any bias introduced depending on the comparison being made and the goals of the evaluation. The population in this large managed care setting is diverse,²² but we were unable to perform many subgroup analyses. This will be another important area for future research. Finally, rates of toxicity are

likely to be a function not only of the type of regimen but also of doses and their density versus reductions and numbers of cycles completed. In future research, we will extend the algorithm to be able to predict the probability of toxicity on the basis of these more detailed components of chemotherapy and update codes to include new International Classification of Diseases, 10th edition codes.

Although our approach should be transportable to new breast cancer treatments and other cancer sites and their specific chemotherapeutic agents, the events included in this algorithm were specifically selected to identify grades 3 and 4 adverse events arising in association with breast cancer chemotherapy based on the regimens currently in use. Finally, although we focus on toxicity during active treatment, there are many other acute as well as persistent and late adverse events, such as fatigue, cognitive difficulties and persistent breast pain.^{34,35} Although likely to be important to quality of life and other outcomes,³⁶ identification of these more subjective complaints may be difficult to capture from electronic health records and may require primary data collection from patients.^{37,38} In fact, efforts are currently underway to validate a set of patient-reported items to capture treatment toxicity from the patient perspective.³⁸ If routinely included in electronic records, such patient-reported toxicity outcomes could be included in future algorithms.

If validated in other samples and settings, algorithms to identify treatment toxicity from electronic data systems could be important in development of risk-stratification tools and comparative and cost-effectiveness evaluations of different regimens in community practice.^{8,18,26} For instance, classifying women by risk of toxicity for a given regimen could lead to more cost-effective use of expensive drugs (eg, Herceptin at \$62,000 in 2012). Overall, methods to quantify and optimize the balance of benefits, harms, and costs of cancer chemotherapy are likely to remain important given the pace of development of new agents. Identification of chemotherapy toxicity could also extend the added value of electronic health records to improving oncology care.

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Appendix

Table A1. Diagnostic, Laboratory, and Procedure Codes Used to Develop the Algorithm to Measure Toxicity of Breast Cancer Chemotherapy During Active Treatment

Toxicity Condition	ICD9 Codes					CPT Codes, Laboratory Values, Drugs
Infection, fever	009.0	009.1	009.2	027.0	027.1	
	027.2	035	038	039	040	
	041	112	114	115	116	
	117	118	130	320	321	
	322	323	480	481	482	
	483	484	485	486	487	
	488	510	511.0	511.1	511.8	
	511.9	513	528.01	590.1	590.10	
	590.11	590.2	590.3	595.0	682.0	
	682.1	682.3	682.4	682.5	682.6	
	682.7	682.8	682.9	686	785.52	
	780.6	780.61				
Diarrhea and dehydration	276.50	276.51	276.52	780.2	458.8	CPT codes: 96360, 96365
	787.91					
Hematologic						
Anemia	284.89-.9	280	285.3	285.9	458.8	Drugs: epoetin, darbepoetin, erythropoietin Laboratory values: hemoglobin < 8.0
Neutropenia	288.00	288.03	288.09	288.5	288.50	Drugs: filgrastim, neupogen Laboratory values: ANC < 1.0, GRAN < 1.0 Laboratory values: ALC < 200/ μ L; < 0.2 $\times 10^9$ /L Laboratory values: total WBC < 2 $\times 10^9$ /L
	288.51	288.59				Laboratory values: PLT < 50,000/ μ L; < 50.0 $\times 10^9$ /L
Thrombocytopenia	287.4	287.5				CPT codes: 36430, 36511, 85014
Transfusion	99.0	99.04	999.89			Laboratory values: WBC > 100,000/ μ L
Leukocytosis	288.6					
Delirium/transient altered mental states*	780.93	780.97	292.2	292.81	293	
	294.9	331.83				
Cardiac (includes embolism/thrombosis, syncope, CHF, MI, arrhythmias)	410	415.1	427.2	427.81	428	CPT code: 33545
	506.1	451.0	453.0-.8	785.0	780.2	
	782.3	451.1	451.2			
Neuropathy	478.11	538	616.81	528	356	Duloxetine hydrochloride, gabapentin, topiramate, amitriptyline, lamotrigine
Severe mucositis	478.11	538	616.81	528.00	528.01	
Liver failure*	570	782.4				
Renal failure*	584					Laboratory values: creatinine > 3.0

Abbreviations: ANC, absolute neutrophil count; CHF, congestive heart failure; CPT, Current Procedural Terminology; GRAN, granulocytes; ICD9, International Classification of Diseases, Ninth Edition; MI, myocardial infarction; PLT, platelets.

* Not included in final algorithm because of low event rate.