Original Article

Avoiding Chemotherapy Prescribing Errors: Analysis and Innovative Strategies

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BACKGROUND: At Freiburg University Medical Center, chemotherapy prescriptions are processed via a computerized physician order entry (CPOE) tool and clinically checked by a designated chemotherapy surveillance team. Any error detected is reported instantly, corrected, and prospectively recorded. The objective of the current study was to gain insight into the causes, potential consequences, and future preventability of chemotherapy prescribing errors. **METHODS:** A detailed analysis of 18,823 consecutive antineoplastic orders placed in 2013 through 2014 was performed. In cooperation with information technology (IT) specialists, the intercepted errors were analyzed for effective future prevention using IT measures. Potential error consequences were determined by case discussions between pharmacists and physicians. **RESULTS:** Within 24 months, a total of 406 chemotherapy prescribing errors were intercepted that affected 375 (2%) of the total orders. Errors were classified as clinically relevant in 279 of the chemotherapy orders (1.5%). In these cases, reduced therapeutic efficacy (0.44%), the need for increased monitoring (0.48%), prolonged hospital stay (0.55%), and fatality (0.02%) were avoided as potential consequences. The most efficient conventional measures for error prevention comprised checking the order history and patient's medical record, and a detailed knowledge of chemotherapy protocols. Of all the errors analyzed, 61% would be avoided through further software development. The improvements identified are implemented through a validated next-generation CPOE tool. **CONCLUSIONS:** The upgraded CPOE tool can be shared across other hospitals to raise safety standards and spread potential benefits across a wider patient population. The current analysis also highlighted that approximately 30% to 40% of errors cannot be avoided electronically. Therefore, pharmacovigilance initiatives remain indispensable. ***Cancer* 2019;125:1547-1557**. © *2019 American Cancer Society.*

KEYWORDS: chemotherapy prescribing, computerized physician order entry, error avoidance, medication safety, pharmacovigilance.

INTRODUCTION

Medical errors were estimated to be the third leading cause of death in the United States in 2013.[1] With approximately 400,000 cases occurring annually in US hospitals, the number of fatalities due to preventable medical errors is equivalent to nearly the entire population of Miami, Florida.[2] However, these figures include documented hospital inpatient cases only and the actual total number of medical errors may be substantially higher. Moreover, medical errors may induce temporary or permanent harm in patients and may have an impact on quality of life. The incidence of cases resulting in serious harm appears to be 10-fold to 20-fold higher than that of cases resulting in lethal harm.[2]

Medication errors represent a common subgroup of medical errors and were found to occur most often during the prescribing stage.[3,4] An evaluation from the Adverse Event Reporting System of the US Food and Drug Administration demonstrated that antineoplastic agents constitute the second most common cause of fatal medication errors.[5]

In antitumor therapy, a growing demand for treatment due to a yearly increase in the number of new cancer cases is associated with an increased workload for health care professionals. Time constraints, together with treatment complexity, make the prescribing of chemotherapy an error-prone process. Due to the narrow therapeutic index of

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cytotoxic drugs, this constitutes a major risk for an already vulnerable patient population. Although overdosing can result in permanent harm to the patient, underdosing may compromise the success of therapy.

Important measures for error prevention include process standardization, decentralized pharmacy services, electronic prescribing databases, and critical incident reporting and root-cause analysis systems. According to the 2012 US Department of Health and Human Services report, hospital incident reporting systems captured only an estimated 14% of the patient harm events experienced by Medicare beneficiaries.[6] Due to incomplete reporting structures and the general paucity of systematic collection of data on "near misses," it is challenging to ascertain an accurate picture of the frequency and seriousness of chemotherapy errors.[7] Therefore, the quality and safety improvements arising from an inefficient reporting culture are suboptimal.

In a previous analysis, we described the prevalence of different error classes in chemotherapy prescribing and the impact of the introduction of a computerized physician order entry (CPOE) tool on error frequency.[8] Addressing the valuable suggestions from our former reviewers, we have performed a more detailed analysis including the potential consequences of the identified errors and with a special focus on future error avoidance. The results will be implemented into upgraded and transferable chemotherapy prescribing software, which currently is under development. This analysis directly integrates research and safety science into clinical practice, thereby addressing a (to the best of our knowledge) unmet need for a novel approach to efficiently improve safety in clinical oncology (see Supporting Table 1).[9,10] The primary objectives of the current study were: 1) to identify the relative frequency, root causes, and potential consequences of chemotherapy prescribing errors; 2) to determine whether errors identified could be prevented using an upgraded CPOE tool; and 3) to develop effective methods for error avoidance by combining software engineering with conventional safety measures.

MATERIALS AND METHODS

Setting

At Freiburg University Medical Center (FUMC), all approved standard adult chemotherapy protocols are accessible via a CPOE database.[11] The protocol content within this database is updated continuously by a designated chemotherapy surveillance team, the Clinical Cancer Research (CCR) group.[8] Physicians use the database to access the protocols and to order chemotherapy. The electronic chemotherapy orders are processed simultaneously by the CCR group and the staff of the pharmacy aseptic production unit. To maintain the highest possible safety standards, both staff groups perform a detailed independent check of each chemotherapy order. Although particular emphasis is placed on issues relevant to sterile production for the pharmacy team, the CCR group principally focuses on clinical accuracy and patient safety.[8] Any detected error is reported to the responsible physician and instantly corrected via the CPOE tool prior to the chemotherapy agents reaching the patient (Fig. 1). When a chemotherapy order is amended, it subsequently is checked again. The CCR group prospectively and systematically records detected and avoided errors in an electronic register within the CPOE database.[8]

The CCR Group and the CPOE System

The CCR group is a unique pharmacovigilance team that has been operating within the hematology and oncology department at FUMC for nearly 15 years. The CCR group ensures safe chemotherapy prescribing in cooperation with the clinical pharmacy.[8] The CCR group consists of 3 pharmacists and 1 accredited accuracy checking technician. The team is located in the clinical complex of the hematology and oncology department at FUMC, and are office and computer based.

The CPOE database used at FUMC features a highly diverse chemotherapy protocol content and an interface to the laboratory and hospital information systems. Electronic alerts are in place for deviations in body weight >5% between cycles and when appropriate for cumulative doses. Dose capping is established for vincristine and for carboplatin, according to the area under curve.

General Parameters and Error Causes

A detailed analysis of the detected and avoided consecutive chemotherapy prescribing errors was performed over a 24-month period (January 2013-December 2014) using IBM SPSS statistical software (IBM Corporation, Armonk, New York). The relevant information from the CCR group error log was retrieved using Structured Query Language. Errors with the potential for immediate patient safety consequences, including the prescribing of an incorrect antineoplastic drug as well as chemotherapy dosing or timing errors (eg, an insufficient gap between

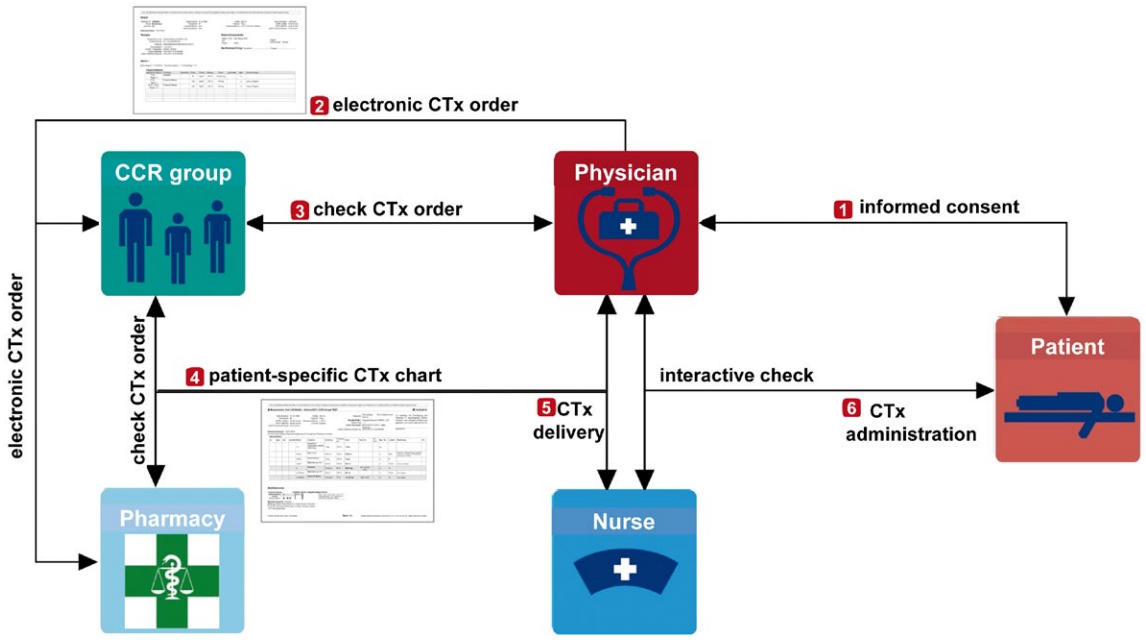

Figure 1. Workflow for central chemotherapy (CTx) management. First, the physician informs the patient about the specific CTx protocol of the planned treatment, including the potential side effects of the respective antineoplastic agents, and obtains the patient's written informed consent. Second, the physician selects the CTx protocol and places an electronic order via the electronic prescribing database. Third, the order is checked by the Clinical Cancer Research (CCR) group (the pharmacovigilance team at Freiburg University Medical Center) and the clinical pharmacy. Any detected error is instantly reported to and corrected by the responsible physician. Fourth, for all verified orders, a patient-specific daily treatment chart is generated by the CCR group. This schedule, comprising CTx and supportive medication in chronological order of administration, is sent via the network printer to the respective point of care. Fifth, at the same time, the compounded CTx products are sent from the pharmacy to the ward or clinic. Finally, once checked and signed by the responsible physician, the treatment chart serves as a valid CTx prescription and a documented record of medicines administration by nurses and physicians.

cycles), were subject to in-depth analysis. Administrative errors (eg, missing patient consent) and minor dose deviations of up to ±5% were excluded.[12,13]

To evaluate each error, the incorrect chemotherapy order, previous orders, and the amended order after pharmaceutical intervention were analyzed. Patient's medical records were accessed as supporting material when appropriate. An overview of the analyzed patient, protocol, and order characteristics is shown in Table 1.[11]

If a chemotherapy order contained multiple chemotherapy agents and the same error occurred in >1 agent (eg, the dose was not tailored to renal function), this was only counted as 1 error.

At FUMC, chemotherapy is nearly exclusively ordered by physicians in training and clinical fellows, with appropriate support measures in place. An evaluation by type of user was not subject to this analysis.

Potential Clinical Consequences and Cost

For each intercepted prescribing error, potential consequences for the patient were discussed and graded in an interdisciplinary consensus between the attending physician (M.E.) and the clinical pharmacist (H.R.). A severity scale, developed from the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) and the medical literature, was applied. Classification ranged from errors considered to be "without consequence" to those considered "possibly lethal" (Table 2).[14-16] In the case of multiple errors per chemotherapy order, only the error with the most severe potential impact was scored. Estimation of the potential consequences was based on the clinical condition of the individual patient at the time of the error. For this purpose, the patient's medical records and laboratory results were consulted. Further clinical evidence, previous rehospitalization data associated with the toxicity of the respective chemotherapy, and data from the medical literature were considered.

For the error categories of "increased monitoring required" and "prolonged hospital stay," the number of potential additional inpatient days or outpatient clinic contacts for extra observation and/or

TABLE 1. Chemotherapy, Order, Protocol, and Patient Characteristics

Parameter	Total (100%)	Incorrect (% from total) [% of Total No. Incorrect]
No. of patients	2436	303 (12.4)
Median age, y	NA	65 (range: 21-89)
Tumor stage		
Local/adjuvant	NA	20 [6.6]
Disseminated/metastatic		283 [93.4]
Degree of RI		
Normal renal function-mild RI (GFR ≥90-60)		212 [70]
Moderate RI (GFR 59-30)	NA	76 [25]
Severe RI: established renal failure (GFR ≤29)		15 [5]
Karnofsky Performance Status		
≥90%	NA	127 [42]
80-60%		165 [54]
≤50%		11 [4]
No. of chemotherapy errors		406
No. of error consequences		396 (10 errors resulted in the same consequence)
No. of chemotherapeutic agents	39,885	508 (1.3)
No. of chemotherapy orders	18,823	375 (2) (25 orders with multiple errors)
Inpatient orders	5944	133 (2.2)
Outpatient orders	12,879	242 (1.9)
Protocol type		
Standard[a]	10,983[c]	152 (1.4)
Nonstandard[b]	5589[c]	202 (3.6)
Clinical trial	2251[c]	21 (0.9)
Protocol complexity		
Noncomplex	11,930	211 (1.8)
Complex[d]	6893	164 (2.4)
No. of administration within a protocol		
First application	6785	108 (1.6)
Consecutive applications	12,038	267 (2.2)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; GFR, glomerular filtration rate; NA, not available. RI, renal impairment.
[a]Standard protocol indicates chemotherapy protocols formally approved by Freiburg University Medical Center.[11]
[b]Nonstandard protocol indicates any modified standard protocol and any protocols not formally approved Freiburg University Medical Center.
[c]Obtained by extrapolation from a separate data collection over 1 month.
[d]Complex protocol indicates ≥3 different chemotherapeutic agents per cycle plus mobilization, conditioning, and high-dose protocols including AML and ALL.

supportive measures was estimated in consensus between the attending physician (M.E.) and clinical pharmacist (H.R.). This estimate was based on the assumption that the errors reached the patients but were noticed prior to discharge. A conservative approach was used for the evaluation of potential patient impact and for the estimation of additional inpatient days, with the less severe potential consequence being recorded when there was any doubt.

Drug expenditure was calculated for the category "solely cost implications" in cooperation with the pharmacy department (S.W.). For other errors with additional potential cost implications, such as overdose errors involving expensive drugs, the cost of the excess unnecessary medication was calculated separately. For errors that may have resulted in reduced therapeutic efficacy, such as underdosing by ≥50% or the omission of a drug, the number of additional inpatient days or outpatient clinic visits required to rectify the chemotherapy error was analyzed.

Error Prevention

Conventional methods for the avoidance of prescribing errors by the physicians ordering chemotherapy were investigated. This included the avoidance of potential errors through thorough knowledge of the respective chemotherapy protocol ordered, consulting the patient's medical records, checking previous chemotherapy orders, and verifying the chemotherapy time schedule. For this purpose, 8 measures for error avoidance were defined and multiple selections per error were allowed. Consulting the previous order was known to be an efficient method of error identification during the clinical accuracy checking process and this was analyzed separately.

Using a cross-functional approach, the errors were analyzed for preventability by software engineering. For this purpose, each error was assessed and graded by an IT specialist (M.R.) together with a clinical pharmacist (H.R.). To demonstrate which errors generally were avoidable through software engineering, error causes were grouped into 18 different categories. Within a category, if ≥70% of the errors could have been prevented by software engineering, the respective error cause was classified as "mostly preventable," whereas if >30% but <70% of errors could have been prevented, the error

TABLE 2. Chemotherapy Errors Prevented and Their Potential Consequences in View of Clinical Impact and Expenditure

Error Category in Order of Increasing Severity	Examples/Cases	No. of Orders Affected (18,823 = 100%)[a]	Further Analyses	Drug Cost, €	No. of Additional Inpatient Days	No. of Additional Clinic Visits
Without consequence	Carboplatin 6% over maximum dose	55 (0.29%)	-			
Solely cost implications	Repeated cetuximab loading on d 8	41 (0.22%)	• Cost	48,088		
Possibly reduced therapy efficacy	R-CHOP intended, rituximab missing	82 (0.44%)	• Additional inpatient d or outpatient clinic contacts for rescheduled chemotherapy administration		19	36
Increased monitoring required	FOLFIRI-panitumumab cycle administered 7 d early	90 (0.48%)	• Additional clinic visits for monitoring • Additional cost for high cost drugs[b]			90
Prolonged hospital stay	Renal impairment; no methotrexate dose adjustment → 77% overdose	103 (0.55%)	• Potential additional inpatient d • Additional cost for high-cost drugs[b]		398	
Possibly lethal	1) Oxaliplatin at a dose of 1373 mg instead of 137.3 mg 2) Doxorubicin at a dose of 603 mg instead of 60 mg 3) Mitoxantrone at a dose of 3320 mg instead of 16.6 mg 4) Paclitaxel at a dose of 4775 mg instead of 191 mg	4 (0.02%)	• Additional cost for high cost drugs[b]	91,700 (or €2,103,980 including romiplostim overdose of €2,012,280)		
Total		375 (2%)		139,788	417	126

Abbreviations: d, day(s); FOLFIRI, leucovorin, 5-fluororuacil, and irinotecan; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.
[a]In the case of multiple errors per order, only the most severe error was accounted for.
[b]Drugs included all-trans retinoic acid (ATRA), arsenic trioxide, bortezomib, carmustine, capecitabine, cidofovir, cytarabine, idarubicin, lenalidomide, intravenous melphalan, paclitaxel, romiplostim, thiotepa, vindesine, and monoclonal antibodies.

cause was classified as "no clear allocation possible." If ≥70% within an error category could not have been avoided by software engineering, the error cause was classified as "mostly not preventable" via the IT tool and its improvement alone.

RESULTS

Error Frequency and Characteristics of the Patients and Protocols

Of 18,823 consecutive chemotherapy orders occurring during the study period, 406 chemotherapy prescribing errors were identified, involving 375 (2%) of the total orders. The error rate was 242 of 12,879 outpatient orders (1.9%) and 133 of 5944 inpatient orders (2.2%). Some prescriptions contained multiple errors. During the study period, the average number of chemotherapy orders processed per patient was 7.7.

Had the errors not been intercepted, 303 (12.4%) of the 2436 patients receiving chemotherapy during this time would have been affected. Repeatedly flawed orders occurred in 73 patients (3%). For the patient found to be most frequently affected by repeatedly flawed orders, 6 prescription errors were detected and prevented.

Of those patients potentially affected, 93.4% had disseminated or metastatic tumors, 64% had some degree of renal impairment, and in 58% of patients the Karnofsky performance status was ≤80% (Table 1).

The error rate in prescriptions following "standard chemotherapy protocols," defined as predesigned chemotherapy protocols formally approved by the FUMC and also regularly published in "The Blue Book," was 1.4%.[11] Error rates in orders of "nonstandard protocols" (ie, any modified standard protocol [eg, by the adaption of chemotherapy doses or modified application

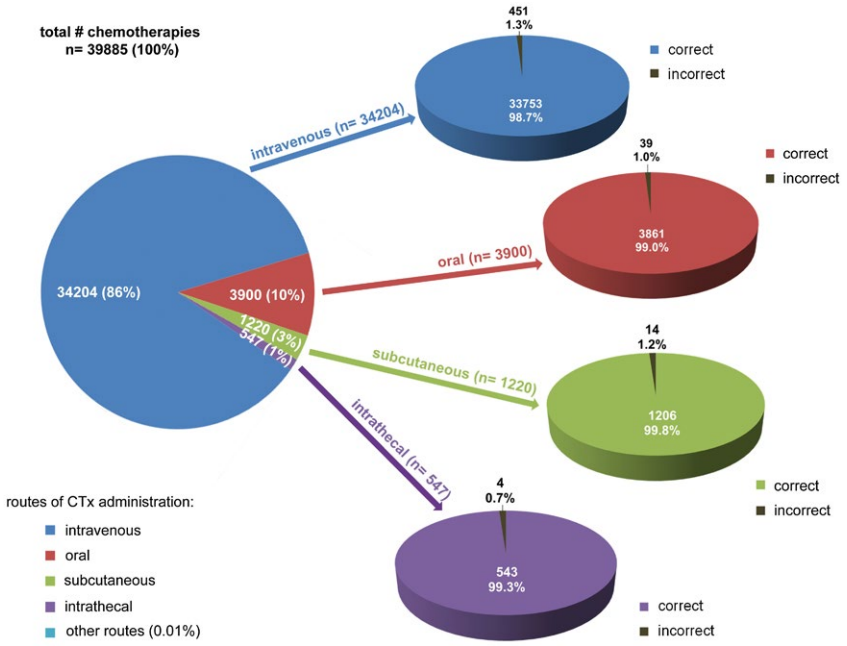

Figure 2. Comparison of chemotherapy (CTx) error rates by different routes of administration. Of the total 39,885 CTx agents ordered in 2013 and 2014, approximately 86% were administered intravenously, 10% were administered orally, 3% were administered subcutaneously, and 1% were administered intrathecally. The error rate was 1.3% in intravenous, 1.0% in oral, 1.2% in subcutaneous, and 0.7% in intrathecal administrations.

schedules]) and "orders forming part of a clinical trial" were 3.6% and 0.9%, respectively.

For complex protocols, defined as protocols with ≥3 agents and all high-dose protocols, the error rate for chemotherapy orders was 2.4%, whereas that for non-complex protocols was 1.8%.

It is interesting to note that orders for consecutive doses or cycles within a protocol were found to be more error prone (2.2%) compared with initial protocol orders (1.6%) (Table 1).

Chemotherapy Agents and Route of Administration

A considerable percentage of the 18,823 chemotherapy orders contained >1 chemotherapy agent, resulting in 39,885 separate orders for chemotherapeutic agents. Within the study period, 508 chemotherapeutic agents (1.3%) were ordered incorrectly, resulting in 1054 inappropriately prescribed single doses (Table 1). The chemotherapy agent most frequently prescribed incorrectly was carboplatin (53 of 1819 orders; 2.9% error rate) followed by intravenous etoposide (37 of 1361 orders; 2.7% error rate). The highest error rate was found for carmustine (23 of 299 orders; 7.7% error rate).

Analysis by route of administration demonstrated error rates for intravenous, subcutaneous, oral, and intrathecal orders of 1.3%, 1.2%, 1.0%, and 0.7%, respectively (Fig. 2).

Error Consequences

The 406 chemotherapy prescribing errors described led to 396 error consequences. This was because in some cases, multiple errors on 1 prescription led to the same consequence. Of these error consequences, 203 (51.3%) would have resulted in an overdose of 256 chemotherapy agents (635 single chemotherapy doses) (Fig. 3 and see Supporting Table 2). The median overdose was 33%, but for 80 chemotherapy agents (31%), the deviation exceeded 50%. The highest overdose detected and avoided was a 1000-fold dose (99,900% overdose) of romiplostim (indicated for the treatment of idiopathic thrombocytopenic purpura and one of the few nononcology drugs ordered via the electronic system), which was erroneously prescribed in milligrams rather than micrograms. Underdosing was the second most commonly prevented error consequence (14.9%). The most frequent cause of dosing errors was full dosing despite a previous dose reduction; other common error causes can be found in Supporting Table 2.

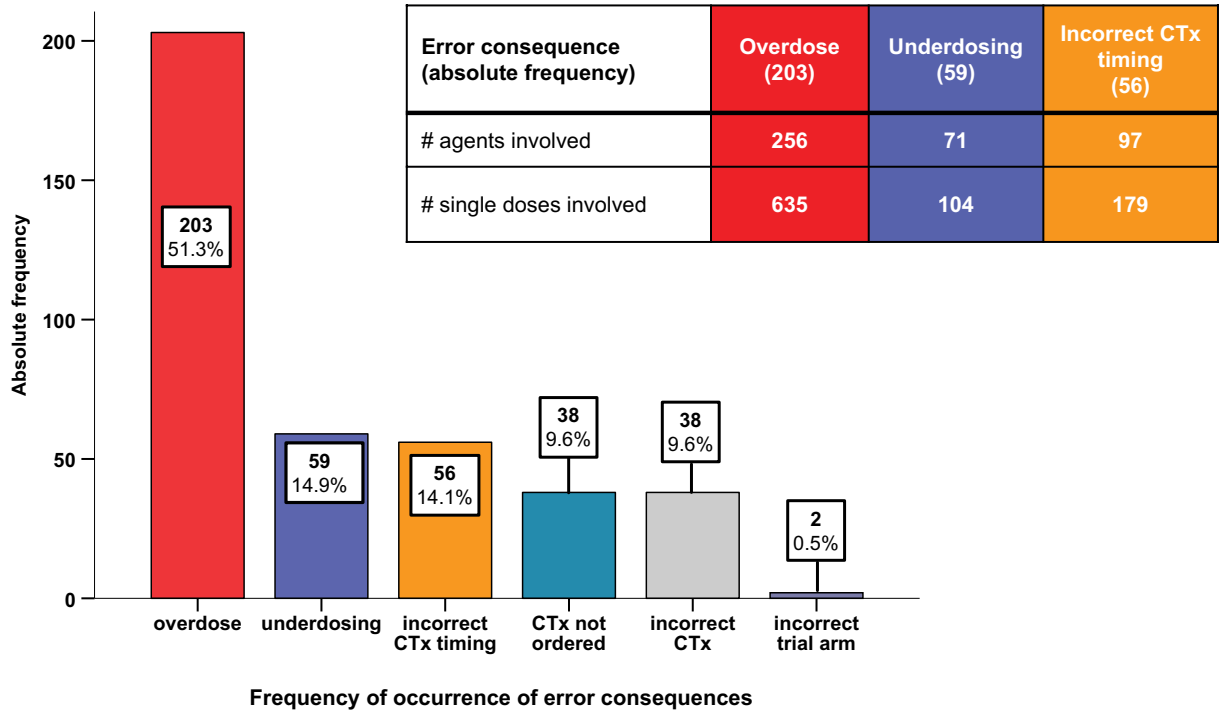

Figure 3. Frequency of occurrence of error consequences. Of the 406 errors analyzed, the total number of error consequences amounted to 396 because in 10 cases 2 different errors on 1 chemotherapy (CTx) order led to the same consequence. For overdosing and underdosing errors, only those errors with a dose deviation of >5% were accounted for. In approximately 51.3% of the cases, errors would have resulted in overdosing, 14.9% in underdosing, and 14.1% in wrong CTx timing. A wrong trial arm was ordered in 0.5% of the errors. The table shown contains information regarding the number of incorrect CTx agents and doses involved. Some CTx orders contain multiple CTx agents per order and for some CTx agents multiple doses are ordered on 1 prescription.

Potential clinical implications

In 103 prescriptions (0.55%), the errors were considered to have potentially resulted in a prolonged hospital stay (Table 2). Other potential consequences identified included an increased requirement for monitoring (90 orders; 0.48%) and a possible reduction in therapeutic efficacy (82 orders; 0.44%) (Table 2). Four potentially lethal chemotherapy errors (0.02%), involving overdoses of oxaliplatin, doxorubicin, mitoxantrone, and paclitaxel, were prevented (Table 2).[17-21]

Potential cost implications

Of the flawed chemotherapy orders, 41 were classified as having only cost implications, without any clinical consequences. Those errors would have resulted in an estimated total increased drug acquisition cost of approximately €48,000. The estimated excess drug acquisition cost for chemotherapy overdoses with potential clinical consequences was €91,700 (or €2,104,000 when including the potential romiplostim overdose). In cases in which it was considered that additional patient observation and supportive therapy would have resulted, an estimated 398 additional inpatient days and 90 outpatient clinic visits were avoided. A further estimated 19 inpatient days and 36 outpatient clinic contacts arising from rectification of omitted therapies were efficiently avoided (Table 2).

Reasons for Errors and Error Prevention

To develop appropriate strategies for error prevention, it was essential to identify the reasons why the respective errors occurred. For this purpose, error causes were divided into 18 categories. The most frequent error causes were overlooked dose modifications of previous orders (13.5%), followed by modification of protocols or missing standard protocols (11.6%). Shortened intervals between doses (10.3%), disregarding of loading dose rules for antibodies (7.4%), and dose adaptions for renal function (5.9%) also were common. Within the electronic chemotherapy prescribing process, chemotherapy doses are calculated by the CPOE tool and verified by the prescribing physician by transcription into the respective fields. Dose transcribing errors formed the third least common error

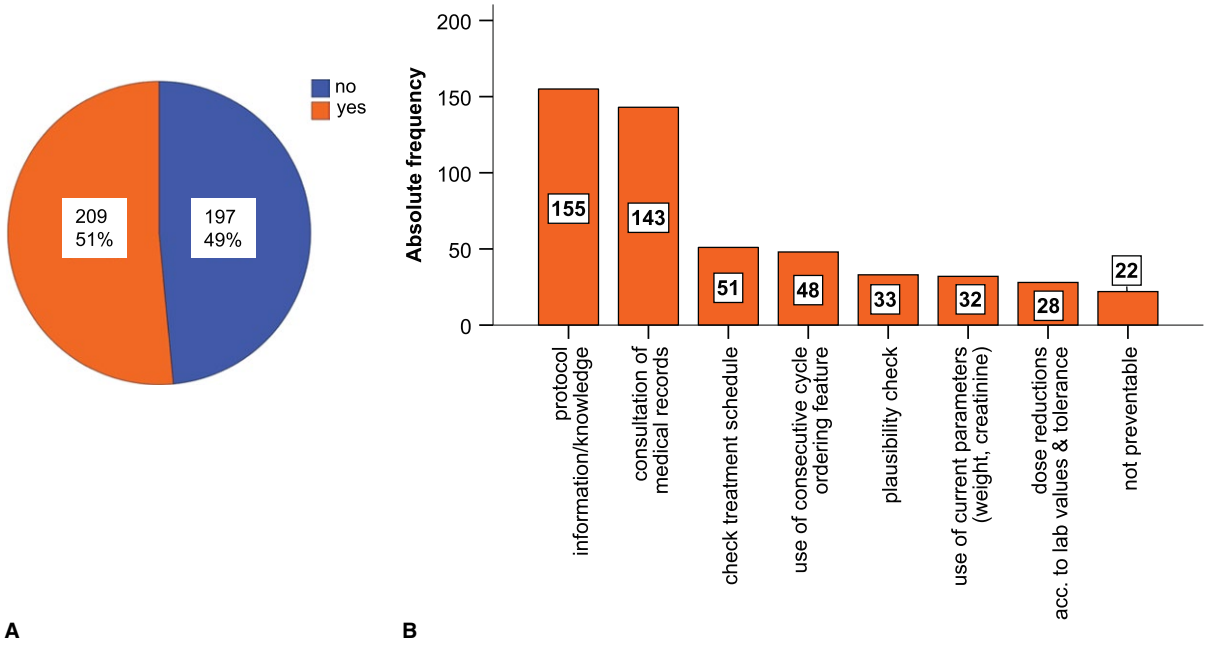

Figure 4. Error avoidance by conventional measures. (A) Error avoidance through consultation of the previous order. Approximately 51% of the errors could have been avoided by consulting the ordering history or previous chemotherapy order. (B) Error avoidance by the efficacy of other conventional measures. The specification of multiple measures for error avoidance per error was allowed. The most efficient conventional measure for error avoidance, apart from viewing of the ordering history (as shown in panel A), was thorough protocol knowledge, which could have avoided an error in 155 of the 406 cases. Another valuable measure was consultation of the medical records, which could have avoided an error in 143 cases.

category (2.2%). However, all 4 errors that were classified as potentially lethal (Table 2) fell into this category.

There were no errors resulting from the CPOE system itself or misprogramming of the CPOE system identified in the 2 years analyzed.

Error prevention by conventional measures

Of the 406 chemotherapy prescribing errors, 209 (51%) were considered preventable by consulting the previous chemotherapy order (Fig. 4A). This check could have assisted in intercepting errors such as early cycle repetition, wrong protocol day ordered, incorrect body weight or height, missed previous dose adaptions, and incorrect protocol selection. Thorough knowledge of the chemotherapy protocol and examination of the patient's medical records could have contributed to an error-free prescription in 155 cases (38%) and 143 cases (35%), respectively (Fig. 4B). Of the 22 errors classified as not preventable by other conventional measures (Fig. 4B), 10 cases were part of the 51% that could have been prevented by consulting the previous order (Fig. 4A). Of the remaining 12 errors, 7 resulted from orders lacking a standard protocol (ie, an approved predesigned treatment schedule for the respective therapy). In 2 cases, current but not the most recent laboratory parameters were used. In another 2 cases, the prescribers' knowledge of dosing rules for antibodies appeared deficient and, in 1 case, the patient's adapted body weight was calculated incorrectly.

Error prevention by software engineering

Using upgraded software with increased safety features, 249 of the prescribing errors (61%) could have been prevented and 20 (5%) were considered less likely to occur. However, for the remaining 137 prescribing errors (34%), avoidance via software enhancement was considered unachievable at present (Fig. 5A).

Nine (50%) of the 18 categories of error cause, as shown in Figure 5B on the x-axis, were considered mostly preventable. As an example, dose adjustments for a patient's current degree of renal impairment can be suggested by the electronic prescribing database. To avoid major overdosing errors, it is possible to set up dose alerts for exceeding predefined maximum doses. The transcription of the calculated doses can be performed electronically. These last 2 points are particularly relevant to the 4 errors classified as potentially lethal. Four categories were rated as mostly not preventable by means of an upgraded software tool, such as wrong protocol selection

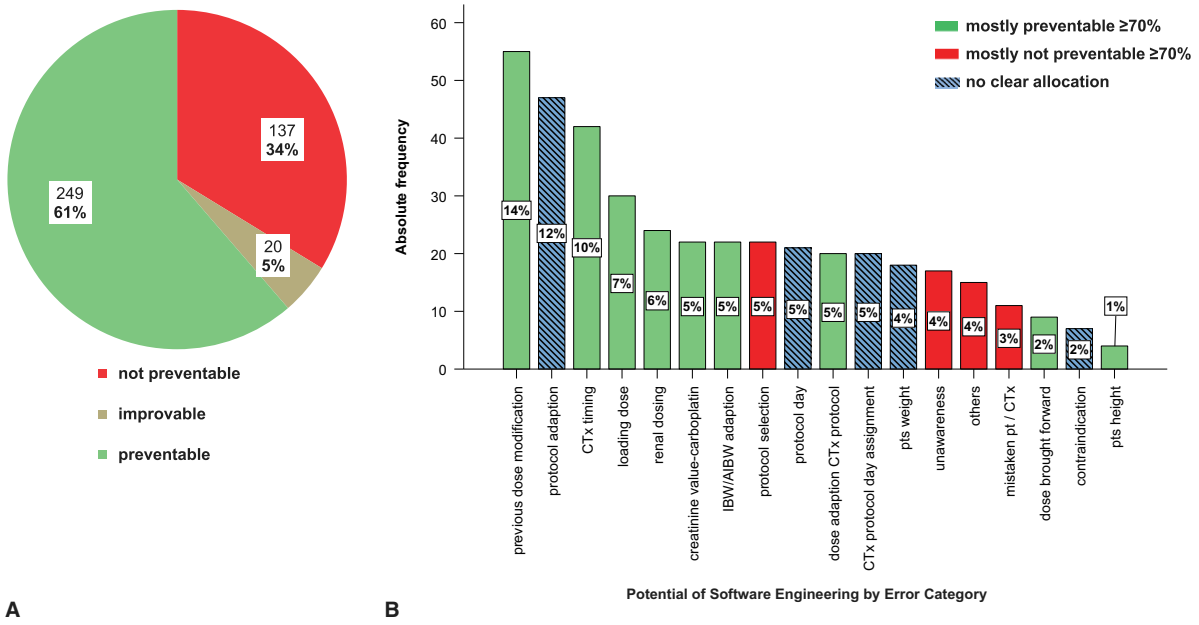

Figure 5. Error prevention by software engineering. (A) Error prevention through the potential of software engineering. The number and percentage of chemotherapy (CTx) ordering errors that were preventable, improvable, and not preventable by an upgraded software tool for CTx ordering. (B) The potential of software engineering by error category. Green bars indicate mostly preventable (eg, the respective error category could have been avoided by software engineering in ≥70% of cases). The most frequent error category, "previous dose modification," occurred in approximately 14% of the errors analyzed. Errors of this type could very efficiently be avoided by a feature pointing out modifications from the standard chemotherapy protocol. For the bars indicated in red, error prevention by software upgrade was not achievable for ≥70% of the cases. An example for a mostly not preventable error category would be "protocol selection" (eg, if the wrong CTx protocol initially was selected). For the error categories indicated in blue, no clear allocation was possible. AIBW indicates adapted ideal body weight; IBW, ideal body weight; pt: patient.

in the first chemotherapy order. For the remaining 5 categories, no clear allocation was possible (Fig. 5B).

DISCUSSION

Prescribing errors are common, but largely can be prevented before drug administration to the patient if appropriate safety structures are in place. Clinical pharmacists play a pivotal role in this error avoidance, designing safety structures and teaching other health care staff.[9,14,17]

A combination of professional education, informatics, and financial incentives for prescription screening have been shown to improve the prescribing safety of nonsteroidal anti-inflammatory drugs and selected antiplatelet agents in primary care.[22] This approach demonstrates parallels with the successful error prevention strategy at FUMC, at which a CPOE tool for chemotherapy ordering is used and an additional clinical accuracy check is performed by a pharmacovigilance team.[8] The errors detected and prevented by this approach potentially could have affected approximately 12.4% of patients for whom chemotherapy orders were placed during 2013 through 2014. By reason of tumor diagnosis, comorbidities, predominantly advanced patient age, tumor stage, and the use of potent antineoplastic drugs with a narrow therapeutic safety margin, the patient population potentially affected was considered particularly at risk if errors remained undetected.

For 2013 through 2014, we prospectively reviewed 18,823 consecutive chemotherapy prescriptions at FUMC. The 2% error rate identified lies within the range previously described (see Supporting Table 1).[23-25] Nevertheless and most important, our analysis demonstrates that these errors all were efficiently eliminated prior to reaching the patient.

Ranchon et al identified the following risk factors for anticancer chemotherapy dose prescribing errors: protocols involving carboplatin, protocols with >3 drugs, and protocols requiring at least 1 modification.[13] In the current analysis, the antineoplastic agent with the highest number of prescribing errors also was found to be carboplatin, suggesting that doses calculated from recent pharmacokinetic parameters present a particular risk of

error. Taking ordering frequency into consideration, the highest error rate was found for carmustine. In clinical practice, a dose adaption of carmustine in high-dose protocols according to ideal or adapted ideal body weight is performed. Neglecting to apply or incorrectly applying this dosing rule was the root cause of this higher error rate in the current analysis. This is in keeping with the findings of others, who identified adaptions such as dose capping as a risk factor for medication errors.[13] The increased risk described for complex protocols, which we defined as those including ≥3 chemotherapy agents, and for modified protocols, also was identified in the current study.

Gandhi et al demonstrated that approximately 75% of all chemotherapy errors have a potential for adverse drug events.[23] After excluding errors classified as "cost only" and "without consequence" from the 2% of errors reported in the current study, the remaining 1.5% were classified as clinically relevant.

For each prevented error that potentially could have resulted in a prolonged hospital stay, the number of additional inpatient days was estimated by interdisciplinary consensus including an attending physician and a clinical pharmacist. Of the 103 errors classified as potentially prolonging hospital stay, the estimated total of additional inpatient days was 398 days based on the assumption that the errors reached the patients but were noticed prior to discharge. Had the patients been discharged and these errors gone unnoticed, this could have resulted in emergency hospital admissions, a prolonged inpatient stay, or even death. This could impact patient safety in terms of increased morbidity and mortality as well as impacting the patient's quality of life.

An investigation of errors reaching the patients was not included in the current study but also would be of interest. Root cause analysis of such errors is performed continuously at FUMC to identify and implement safety improvements and to reduce the risk of disease recurrence. We have reported on this in a previous analysis.[8]

The recommended conventional measures for error prevention identified herein can be applied by any appropriately trained and accredited prescribing physician. A particular strength of the current analysis was the combination of potential error consequences and error causes, including preventability. This approach enables the prioritization of steps for software improvement based on the severity of the respective preventable errors. Of the 4 errors classified as potentially lethal, 3 errors can be prevented by automated dose transcription of the calculated chemotherapy dose. This feature already has been implemented into the new prescribing software used at our center.

The romiplostim error (Table 2) was due to incorrect use of the software by the ordering physician, in which an inappropriate manual manipulation of the unit "µg/kg" as defined in the romiplostim protocol was performed within the prescribing process ("µg/kg" was changed to "mg/kg"). This could be prevented by a software upgrade that blocks or restricts manual entries for the unit field or by defining maximum doses within the CPOE system.

According to our experience, a state-of-the-art CPOE system needs to have a clear layout and be simple for both new and/or occasional users to use. Key features are protocol content, automated dose calculation without the need for manual manipulations, and dose alerts for maximum doses, whereas "overalerting" needs to be avoided. Features to point out dose modifications of the previous cycle or renal dosing also may be beneficial. Certainly, all users need to be instructed regarding how to use the software correctly, which is meticulously and regularly ensured at FUMC.

Previous literature regarding error reduction through novel technology highlighted that the use of CPOE may introduce new types of errors.[10,26] The first CPOE system used at FUMC was implemented in 2006. The new-generation ordering tool is developed from the previously used software and thus benefits from the long-term experience of its application in clinical practice. Nevertheless, further work is required to continuously upgrade and validate the new chemotherapy ordering database, including detailed error analysis from the data generated via this new electronic ordering tool.

Conclusions

The results of the current study demonstrate that consideration of ordering history and consultation of patient's medical records in addition to thorough knowledge of chemotherapy protocols are very effective conventional measures for error prevention in the high-risk prescribing process of antineoplastic drugs.

The analysis of potential clinical consequences in combination with analysis of error prevention by software engineering enables the prioritization of identified target areas of risk for improvement. According to the results of the current study, approximately 61% of chemotherapy prescribing errors are preventable through software engineering. With these enhancements readily transferable to external centers, there is the potential to increase chemotherapy safety in a wider patient population. However, despite software modifications, an estimated 39% of errors would remain unidentified and uncorrected by the CPOE system. The pharmacovigilance and ward

pharmacist teams remain of key importance in intercepting such errors, thus making an essential contribution to improving the safety within this high-risk patient population.

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CONFLICT OF INTEREST DISCLOSURES

Manfred Jung is cofounder and co-owner of K-metics, a biotech company developing anticancer drugs that was not related to the current study.

AUTHOR CONTRIBUTIONS

Heike Reinhardt: Conceptualization, data curation, formal analysis, funding acquisition, investigation, project administration, methodology, validation, visualization, writing–original draft, and writing–review and editing. **Petra Otte**: Data curation and writing–review and editing. **Alison G. Eggleton**: Formal analysis and writing–review and editing. **Markus Ruch**: Validation, software, and writing–review and editing. **Stefan Wöhrl**: Investigation and writing–review and editing. **Stefanie Ajayi**: Writing–review and editing. **Justus Duyster**: Resources and writing–review and editing. **Manfred Jung**: Conceptualization, supervision, and writing–review and editing. **Martin J. Hug**: Conceptualization and writing–review and editing. **Monika Engelhardt**: Conceptualization, formal analysis, funding acquisition, methodology, project administration, resources, supervision, validation, visualization, writing–original draft, and writing–review and editing.

REFERENCES

1. Makary MA, Daniel M. Medical error—the third leading cause of death in the US. *BMJ*. 2016;353:i2139.
2. James JT. A new, evidence-based estimate of patient harms associated with hospital care. *J Patient Saf*. 2013;9:122-128.
3. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA*. 1995;274:29-34.
4. Serrano-Fabia A, Albert-Mari A, Almenar-Cubells D, Jimenez-Torres NV. Multidisciplinary system for detecting medication errors in antineoplastic chemotherapy. *J Oncol Pharm Pract*. 2010;16:105-112.
5. Phillips J, Beam S, Brinker A, et al. Retrospective analysis of mortalities associated with medication errors. *Am J Health Syst Pharm*. 2001;58:1835-1841.
6. US Department of Health and Human Services. Hospital incident reporting systems do not capture most patient harm. Report OEI-06-09-00091. https://oig.hhs.gov/oei/reports/oei-06-09-00091.asp. Accessed May 12, 2018.
7. Fernandez CV. Can we prevent cytotoxic disasters? *Br J Haematol*. 2000;108:464-469.
8. Markert A, Thierry V, Kleber M, Behrens M, Engelhardt M. Chemotherapy safety and severe adverse events in cancer patients: strategies to efficiently avoid chemotherapy errors in in- and outpatient treatment. *Int J Cancer*. 2009;124:722-728.
9. Weingart SN, Zhang L, Sweeney M, Hassett M. Chemotherapy medication errors. *Lancet Oncol*. 2018;19:e191-e199.
10. Mattsson TO, Holm B, Michelsen H, Knudsen JL, Brixen K, Herrstedt J. Non-intercepted dose errors in prescribing anti-neoplastic treatment: a prospective, comparative cohort study. *Ann Oncol*. 2015;26:981-986.
11. Engelhardt M, Berger D, Mertelsmann R, Duyster J, eds. The Blue Book: Chemotherapy Manual, Hematology/Oncology. 6th ed. Heidelberg, Germany: Springer Medizin Verlag; 2016.
12. Reinhardt H, Trittler R, Eggleton AG, et al. Paving the way for dose banding of chemotherapy: an analytical approach. *J Natl Compr Cancer Netw*. 2017;15:484-493.
13. Ranchon F, Moch C, You B, et al. Predictors of prescription errors involving anticancer chemotherapy agents. *Eur J Cancer*. 2012;48:1192-1199.
14. National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP). Types of medication errors. February 20, 2001. https://www.nccmerp.org/types-medication-errors. Accessed February 13, 2017.
15. Schneider PJ, Gift MG, Lee YP, Rothermich EA, Sill BE. Cost of medication-related problems at a university hospital. *Am J Health Syst Pharm*. 1995;52:2415-2418.
16. Ranchon F, Salles G, Spath HM, et al. Chemotherapeutic errors in hospitalised cancer patients: attributable damage and extra costs. *BMC Cancer*. 2011;11:478.
17. Soloni P, Compostella A, Carli M, Bisogno G. A case of oxaliplatin overdose. *Pediatr Blood Cancer*. 2009;52:902-903.
18. Sanofi-Aventis. Eloxatin FDA full prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021759s012lbl.pdf. Accessed October 6, 2017.
19. Medac GmbH. Medical information. Doxorubicin hydrochloride 2 mg/ml solution for infusion–summary of product characteristics: electronic Medicines Compendium. https://www.medicines.org.uk/emc/medicine/24588#OVERDOSE. Accessed October 6, 2017.
20. Hospira Medical Information. Mitoxantrone (mitozantrone) 2 mg/ml sterile concentrate–summary of product characteristics: electronic MedicinesCompendium.https://www.medicines.org.uk/emc/medicine/10050#OVERDOSE. Accessed October 6, 2017.
21. Hospira Medical Information. Paclitaxel 6 mg/ml concentrate for solution for infusion–summary of product characteristics: electronic Medicines Compendium. https://www.medicines.org.uk/emc/medicine/15842#OVERDOSE. Accessed October 6, 2017.
22. Dreischulte T, Donnan P, Grant A, Hapca A, McCowan C, Guthrie B. Safer prescribing–a trial of education, informatics, and financial incentives. *N Engl J Med*. 2016;374:1053-1064.
23. Gandhi TK, Bartel SB, Shulman LN, et al. Medication safety in the ambulatory chemotherapy setting. *Cancer*. 2005;104:2477-2483.
24. Nerich V, Borg C, Villanueva C, et al. Economic impact of prescribing error prevention with computerized physician order entry of injectable antineoplastic drugs. *J Oncol Pharm Pract*. 2013;19:8-17.
25. Voeffray M, Pannatier A, Stupp R, Fucina N, Leyvraz S, Wasserfallen JB. Effect of computerisation on the quality and safety of chemotherapy prescription. *Qual Saf Health Care*. 2006;15:418-421.
26. Meisenberg BR, Wright RR, Brady-Copertino CJ. Reduction in chemotherapy order errors with computerized physician order entry. *J Oncol Pract*. 2014;10:e5-e9.