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Non-intercepted dose errors in prescribing anti-neoplastic treatment: a prospective, comparative cohort study

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Background: The incidence of non-intercepted prescription errors and the risk factors involved, including the impact of computerised order entry (CPOE) systems on such errors, are unknown. Our objective was to determine the incidence, type, severity, and related risk factors of non-intercepted prescription dose errors.

Patients and methods: A prospective, comparative cohort study in two clinical oncology units. One institution used a CPOE system with no connection to the electronic patient record system, while the other used paper-based prescription forms. All standard prescriptions were included and reviewed. Doses were recalculated according to the guidelines of each institution, using the patient data as documented in the patient record, the paper-based prescription form, or the CPOE system. A non-intercepted prescription dose error was defined as ≥10% difference between the administered and the recalculated dose.

Results: Data were collected from 1 November 2012 to 15 January 2013. A total of 5767 prescriptions were evaluated, 2677 from the institution using CPOE and 3090 from the institution with paper-based prescription. Crude analysis showed an overall risk of a prescription dose error of 1.73 per 100 prescriptions. CPOE resulted in 1.60 and paper-based prescription forms in 1.84 errors per 100 prescriptions, i.e. odds ratio (OR) = 0.87 [95% confidence interval (CI) 0.59–1.29, $P = 0.49$]. Fifteen different types of errors and four potential risk factors were identified. None of the dose errors resulted in the death of the patient.

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Conclusion(s): Non-intercepted prescribing dose errors occurred in <2% of the prescriptions. The parallel CPOE system did not significantly reduce the overall risk of dose errors, and although it reduced the risk of calculation errors, it introduced other errors. Strategies to prevent future prescription errors could usefully focus on integrated computerised systems that can aid dose calculations and reduce transcription errors between databases.

Key words: oncology, prescription practices, patient safety, medication error, adverse event, CPOE

introduction

Medication errors continue to pose a significant challenge to the safety of modern healthcare. Anti-neoplastic drugs have narrow therapeutic indexes, complex dosing schedules, and significant toxicities even at recommended dosing ranges. Administration and prescription of anti-neoplastic drugs are known as error-prone, high-risk processes with the potential to harm patients.

The frequency of medication errors in the cancer population has been reported to be as high as 8% [1], yet very few medication errors actually reach patients and cause harm [2]. Nevertheless, anti-neoplastic drugs are the second most common cause of deaths due to medication errors [3]. Prescription is a critical stage in the medication process, and a dose error at this stage carries a high risk for causing patient harm. Anti-neoplastic overdosing may result in irreversible harm to patients [4].

Computerised order entry (CPOE) systems are widely regarded as being effective in reducing hospital medication errors [5–7], yet few studies have investigated the impact of CPOE systems in the oncology setting and results are conflicting. While some reports indicate that CPOE systems eliminate dose errors [8], others conclude that CPOE systems may also introduce new medication risks [9, 10].

The development and implementation of effective ways to reduce medication errors require knowledge of the incidence of errors as well as an understanding of their causes and associated factors. Previous studies have focused on the incidence, type, and severity of prevented medication errors with potential to harm patients [9, 11]. This study have focused on the non-intercepted medication errors with the future perspective of, suggesting and evaluating changes in the prescribing process, aiming at reducing the risk of non-intercepted dose errors.

Our aim was to (i) evaluate the incidence and severity of anti-neoplastic medication prescribing errors that resulted in an incorrect dose being administered to the patient, and (ii) to examine potential risk factors associated with these errors, including organisational aspects (CPOE versus non-CPOE), patient characteristics, and treatment regimen.

materials and methods

The study was a prospective observational comparison of two cohorts, followed simultaneously at two Danish Clinical Oncology Units located at Odense University Hospital (OUH), the Region of Southern Denmark, and Herlev Hospital (HH), the Capital Region of Denmark, from 1 November 2012 to 15 January 2013. The units provide non-surgical management of solid malignancies.

One institution, OUH, used a paper-based prescription form for communication between the nursing staff, the prescribing doctor, and the hospital pharmacy. HH used paper-based prescription forms between the nursing staff and the doctors and a CPOE system for communication between the doctors and pharmacy. The CPOE system has two main purposes. First, to eliminate ambiguity in the ordering of anti-neoplastic treatment and to provide decision support by introducing dose calculations, dose limits, and standard doses. Secondly, to provide up-to date information on the treatment regimen and standard operating procedures at point of care. The system was developed locally, and has been continuously modified to accommodate new treatments and protocols (see supplementary Material S1, available at *Annals of Oncology* online).

The review covered all standard regimen anti-neoplastic drug prescriptions ordered and issued to ambulatory and inpatients during the study period. Doses were recalculated according to the specific anti-neoplastic regimen dose calculation and dose-adjustment guidelines of each institution (locally adapted national guidelines). Recalculation was based on the patient data documented in the electronic patient record (EHR), the paper-based prescription form (OUH), or the CPOE system (HH) before, or at the time of, prescription. Recalculation was conducted prospectively, with a delay of 1–2 weeks to ensure that chart notes on prescription would have been entered into the EHR. Trained nurses and medical students carried out the primary screening, data collection, and dose recalculation. A physician (first author) was available to answer any questions about the data and recalculation, and any concerns regarding the future safety of the patient were reported immediately to the first author.

All potential dose differences (regardless of the percentage of the dose difference) were listed. These dose differences were then recalculated and evaluated by a physician (first author) to confirm or dismiss the presence of a non-intercepted dose error and thereafter to assess the type and severity of the dose error. The severity was judged retrospectively, with a minimum follow-up of 1 year after prescription.

outcome measure and definition of non-intercepted dose error

The primary outcome was non-intercepted dose error, defined as an unintended ≥10% difference between the actual administered dose and the guideline-based recalculated dose. Thus, prescription of any clearly intended anti-neoplastic drug dosages was allowed regardless of the argumentation.

data collection and potential risk factors

Data were compiled on patient characteristics, prescription-related aspects, and various clinical factors (Table 1). Age and sex groups were calculated using the patient ID number. A prescription was considered 'incomplete' if one or more pre-printed fields were left blank. Time from prescription to administration was calculated using order entry date and treatment administration date (same day or 1 or more days prior). Prescription day was categorised as Friday versus not Friday using the order entry date. The complexity of dose calculation was categorised based on the treatment regimen.

statistical methods

Error rates were compared using χ^2 test. Differences in type were assessed using Fisher's exact test. Potential risk factors were examined using logistic regression. All analyses were adjusted for clustering at the patient ID level,

Table 1. Data collected on factors potentially related to medication errors

Patient characteristics
Patient ID number (includes birth date and sex)
Cancer diagnosis (ICD10)
Hospital (OUH versus HH)
Prescription-related
Status of prescriber (resident versus senior physician)
Anti-neoplastic treatment regime prescribed
Order entry date
Treatment administration date
Completeness of prescription (yes/no)
Inconsistencies between the data in the paper prescription form, the CPOE system or the electronic patient record in terms of
Glomerular filtration rate (measured by Cr-EDTA*)
Weight
Height
Diagnosis
Reduction of anti-neoplastic dose
Treatment regimen
Treatment date
Anti-neoplastic dose
Patient chart review
Anti-neoplastic dose correct according to guidelines (yes/no),
if 'no' then
Administered dose
Correct dose
Episodes of neutropenia and fever before current prescription (yes/no), if 'yes' then
Date of admission
Admission hospital

Cr-EDTA, a measurement of the baseline and post-captopril glomerular filtration rate using chromium-51-labelled ethylenediaminetetraacetic acid.

and interactions of all covariates were included. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed for the final logistic regression model using a backward selection process. The model tested using the goodness-of-fit test. Statistical tests were conducted using a two-sided alpha risk level of 0.05. STATA version 11.2 was used for the analysis.

results

A total of 5767 anti-neoplastic prescriptions were reviewed during the study period, i.e. 3090 prescriptions from OUH and 2677 prescriptions from HH. The prescriptions were written for a total of 2114 individual patients (further details in supplementary Material S2, available at *Annals of Oncology* online).

The overall rate of non-intercepted prescription dose errors was 1.73 per 100 prescriptions, with a rate of 1.84 per 100 prescriptions at OUH and 1.60 per 100 prescriptions at HH. Crude analysis revealed no statistically significant difference between the two hospitals [OR = 0.87 (95% CI 0·59–1.29, $P = 0.49$)].

Fourteen different types of dose errors were identified (Table 2). OUH had significantly ($P < 0.00$) more errors than HH due to incorrect calculation of body surface area and of number of tablets. HH had a more even distribution of dose errors across the 14 categories, with significantly more errors than OUH related to incorrect dose reduction ($P = 0.03$), incorrect starting dose ($P = 0.01$), and full dose given despite prior reduction ($P = 0.03$) (examples in supplementary Material S3, available at *Annals of Oncology* online).

None of the non-intercepted dose errors resulted in or contributed directly to the death of a patient. Four 'overdose' errors were judged as having potentially contributed to extended hospital stay or increased side-effects, including an episode of severe febrile neutropenia in one patient. Three of these errors were due to using an incorrect glomerular filtration rate (GFR) in prescriptions issued for two different patients at OUH; the fourth error was in a patient at HH who received a full dose despite prior reduction. All these patients were followed to ensure that the errors were not repeated. One 'under-dose' error at OUH was judged as potentially having contributed to lack of treatment efficacy, as the dose given was <60% of the correct dose, and disease progression was diagnosed at the following clinical control.

Table 3 shows the univariate analysis of all potential risk factors for non-intercepted prescription dose errors. Dose errors were significantly higher for female patients than male patients ($P = 0.02$), but no difference was seen with regard to patient age. We found no significant differences in the error rate according to hospital, completeness of prescription, seniority of prescriber, time from prescription to drug administration ($P = 0.57$), or prescription day. However, prescriptions with a dose error had significantly more inconsistencies in GFR, weight, and dose (all $P < 0.00$) than the prescriptions without dose error. Dose error was significantly lower in prescriptions with a fixed dose ($P = 0.02$) and higher in prescriptions where doses were calculated using both GFR and body surface area ($P = 0.02$).

Table 4 show the multivariate analysis. As above, non-intercepted prescribing dose errors were more likely in prescriptions issued for female patients, and where prescription data on GFR, weight, or dose were inconsistent with information in the patient records or the corresponding paper prescription (OR of ~2). Prescriptions based on complex dose calculations [i.e. on both GFR and body surface area (BSA)] had an OR of 9 for errors, compared with fixed dose prescriptions.

discussion

Our study showed that 1.7% of prescriptions for anti-neoplastic drugs that were issued to patients had dose errors that resulted in at least 10% over- or under-medication. We found no statistically significant difference in the rate of error between the institution using a CPOE system and the institution using paper prescription forms.

An overall rate of 1.73 errors per 100 prescriptions may appear low compared with the rates reported in the literature, which range from 2% to 20% [1, 2, 8, 9, 12–14]. All these studies included intercepted errors. Some also assessed non-intercepted errors [9] i.e. by collecting voluntary reporting of incidents [2, 12] by the staff, but none of the studies were designed solemnly to identify non-intercepted errors. The results of these types of studies depend very much on the definition of medication error used, the method, and the setting. Our rate may be

Table 2. Types of non-intercepted dose error in two clinical oncology units using different administrative systems for prescriptions

Type of dose error	Total number of errors	Computerised order entry (Herlev)	Paper-based forms (Odense)	*P*-value
Incorrect dose reduction	9	7	2	**0.03**
Full dose given despite prior dose reduction (i.e. 100%–75%–100%)	9	7	2	**0.03**
Failure to recalculate dose despite more than 10% change in body weight	14	8	6	0.26
Dose-banded dose >10% of exact dose	5	5	0[a]	–
Dose reduction by a percentage of a prior reduced dose (i.e. 100%–75%–37.5%)	2	1	1	1.00
Incorrect starting dose	6	6	0	**0.01**
Difference in patient's height	2	2	0	0.18
Blood test results not accounted for	2	1	1	1.00
Incorrect glomerular filtration rate (GFR)	10	2	8	0.18
Missed loading dose after paused treatment	2	2	0	0.18
Treatment at incorrect AUC[b]	2	1	1	1.00
Incorrect calculation of body surface area	19	0	19	**<0.01**
Failure to increase dose after first well tolerated treatment as according to guideline	1	0	1	0.43
Incorrect calculation of number of tablets in oral treatment	15	0	15	**<0.01**
Dose not prescribed in electronic record, no note of physician's visit	2	1	1	1.00
	100	**43**	**57**	

The bold values are significant within a 95% confidence interval using Fisher's exact test.
[a]OUH did not use dose banding and thus had no errors of this kind (see some examples of error types in supplementary Material S3, available at *Annals of Oncology* online).
[b]Area under the curve (AUC).

regarded as low considering the complexity of anti-neoplastic treatment, or as high considering the potential severity of harm from non-intercepted errors.

We were surprised to find no significant difference in error rate between the computerised and paper systems, as CPOE systems have been reported to reduce general prescribing errors for anti-neoplastic agents by up to 100% [8, 11, 12, 15–17]. In contrast, a study identified 22 types of potential medication error risks when using CPOE systems [10] and a recent study found anti-neoplastic prescription error rates of 7% even when using a CPOE system [9]. Several factors could explain our findings. The CPOE system at Herlev operated in parallel with the EHR without data sharing and thus did not eliminate the risk of transcription errors between the EHR and the CPOE system. Furthermore, the CPOE system provided no background documentation such as the most recent measurements of GFR or body weight. The CPOE system may also have eliminated some of the checks conducted by the pharmacy when processing paper prescriptions. Our findings emphasize the need for a user-centred incremental development [18] of CPOE systems to ensure safety.

The oncology unit using paper-based prescriptions had a significantly higher number of dose errors due to incorrect calculations, especially of BSA and number of tablets required. On the other hand, although the CPOE system provided automatic calculations, it allowed the doctor to prescribe any dose to the patient including re-prescription of a 100% dose despite prior reduction. The prescriptions were also communicated and handled differently by the hospital pharmacies. The pharmacy at OUH was given an overview of the prior prescriptions when handling the paper form, thus in theory providing a double check, whereas the pharmacy at HH would have to check such information manually. Safety may be improved at both institutions by constituting (HH) or expanding (OUH) pharmacy checks of prescriptions before processing, as previously shown by others [12]. Allowing full access to the EHR by pharmacy staff could enable this. Errors due to incorrect GFR were seen at both hospitals, some due to transcription errors and others due to the Cr-EDTA-based GFR results being presented as both measured and adjusted. Thus, the prescribing doctor could inadvertently use the adjusted GFR instead of the measured GFR, although the measured GFR was emphasized in the CPOE system. Most treatment regimens require a dose recalculation if patient weight changes by more than 10%, and omitting recalculation in such cases was a common error at both hospitals. This was probably explained by the hospital workflow in which nurses measured body weight and enter the result into the patient EHR. The prescribing doctor may overlook or fail to document the decision to disregard the change in body weight, especially when prescriptions are written before the patient visit.

Judging the severity of the non-intercepted dose errors proved very difficult. The NCC MERP harm index categories E through I were less meaningful in this population that consisted of patients with a possible poor prognosis, highly toxic treatment regimens and great variation in frequency of side-effects even at correct doses. Some patients tolerated overdosing well and may

Table 3. Non-adjusted univariate analysis of potential risk factors for non-intercepted prescription dose errors

	Prescriptions with dose error ($N = 100$)	Prescriptions without dose error ($N = 5676$)	P-value
Patient gender			
Male	31	2400	
Female	69	3267	**0.02**
Patient age			
≤75 years	84	4863	
>75 years	16	804	0.61
Hospital			
Odense	57	3033	
Herlev	43	2634	0.49
Prescription completeness			
Complete	38	2364	
Incomplete	62	3303	0.46
Status of prescriber			
Resident	49	3044	
Senior	51	2623	0.35
Time from prescription to administration			
Same day	29	1793	
>1 day	71	3874	0.57
Inconsistency between prescription, chart or CPOE system on			
Glomerular filtration rate (GFR)	13	338	**0.004**
Height	14	531	0.12
Weight	47	1812	**0.001**
Dose	21	547	**<0.001**
Diagnosis	4	130	0.262
Regimen	4	148	0.390
Treatment date	5	218	0.553
Reduction of dose	4	147	0.383
Prescription day			
On Fridays	22	1179	
Not on Fridays	78	4488	0.770
Complexity of calculation			
Fixed dose	1	402	**0.018**
Calculation by weight	2	122	0.917
Calculation by height and weight	71	4188	0.513
Calculation by GFR and body surface area	26	955	**0.016**

Table 4. Multivariate analysis of risk factors for non-intercepted prescription dose errors adjusted for clustering by patient ID

	Number of patients ($N = 5767$)	Odds ratio (95% confidence interval)	P-value
Patient gender			
Male	2431	**0.52** (0.29; 0.96)	0.038
Female	3336	1	
Inconsistency between prescription, chart or CPOE system on			
Glomerular filtration rate (GFR)	351	**2.29** (1.15; 4.56)	0.018
Weight	1859	**2.08** (1.28; 3.36)	0.003
Dose	568	**2.58** (1.49; 4.48)	0.001
Complexity of calculation			
Fixed dose	403	Ref.	
Calculation by weight	124	6.66 (0.58; 75.77)	0.126
Calculation by height and weight	4259	6.42 (0.88; 47.06)	0.067
Calculation by GFR and body surface area	981	**9.06** (1.23; 74.40)	0.030

even have benefitted from the error. Others experienced side-effects but not to any unusual extent. Others were given an under-dose, yet tolerated the treatment poorly and may even have been spared side-effects. Four of the non-intercepted dose errors were judged to have contributed to prolonging of hospital stay, greater side-effects or possibly less effective treatment, but none resulted in the immediate death of the patient.

Our finding that non-intercepted dose errors were more frequent in prescriptions for females could be due to differences in cancer diagnoses and treatment regimens between the sexes. Some regimens require more modification than others, and such protocols have a higher risk of dose error [13]. We did not directly investigate the effect of regimen modification, but focused on possible risk factors that would lead to the need for a modification, believing this would be more beneficial.

Previous studies have found prescriptions by residents to be a risk factor for prescribing error [13, 14], but we found no significant differences according to hospital or to seniority of the prescribing physician. Previous studies have reported prescriptions on Fridays as being at a higher risk of medication error [19], but we did not find this in our study.

Three sources of inconsistency between prescription data sources were found to be significantly associated with medication errors. These were differences in GFR, patient weight, and intended dose documented in the EHR and the paper or CPOE prescription. This is understandable, as dose calculation relies on both patient weight and the measured GFR. Prior studies found that protocols with more than three anti-neoplastic drugs [13, 14] or including carboplatin (where doses are calculated according to GFR) were at higher risk of dose error. We also found that complex dose calculations were associated with a much higher risk of medication error, but our study did not include any prescriptions issuing more than three different anti-neoplastic drugs simultaneously.

strengths and limitations

To our knowledge, it is the first to focus solemnly on non-intercepted dose errors. We prospectively evaluated the prescription process from the prescriber's perspective and to prevent bias,

the findings were not released to the prescribers until several months after the end of data collection. Moreover, we studied two clinical units with different organisational systems but similar patient populations. Finally, follow-up was at least 1 year, thus improving assessment of the outcome of the dose errors.

First, it was restricted to one country and to treatment of solid malignancies. The results may not be generalisable to other oncology settings or health-care systems. We evaluated only one specific CPOE system. Other CPOE systems may perform differently, and the conclusions may not be directly transferable. The data collection was, thus prospective in collection, based on the documentation made in the patient chart, which could have affected both incidence and the judgement of severity. The incidence of non-intercepted dose error was based on a definition of 10% difference, which was chosen by the authors due to the fact that HH used this as a limit of acceptance on dose bands. Severity assessment was made by one physician reviewer; a double reviewer assessment may improve validity of this assessment.

future perspectives

The study findings have prompted several changes at both institutions to improve safety in the prescription process. Changes include, more support and training in making complex dose calculations, reading of GFR results and focus on reducing transcription errors. This could be done in CPOE systems by integrating them with other patient data systems. Previous studies have also found that an additional pharmacist check of the patient record information is valuable [1].

conclusion

Non-intercepted prescription dose errors occurred in 2% of the prescriptions in two Danish clinical oncology units. The parallel CPOE system did not significantly reduce the risk of non-intercepted prescription dose errors. Indeed, while it did reduce the risk of calculation error, it also introduced other types of dose errors. Future strategies to prevent prescription errors should focus on safe implementation of integrated CPOE systems that are user-friendly, support decision making and allow pharmacist to conduct checks of the prescriptions.

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disclosure

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