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Predictors of prescription errors involving anticancer chemotherapy agents

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Abstract

Aim: The majority of medication errors that harm patients relate to the prescribing process. Our study aimed to identify the predictors of prescription errors involving anticancer chemotherapy agents.

Methods: All consecutive antineoplastic prescriptions from June 2006 to May 2008 were analysed, with medication errors being captured. Potential risk factors for medication prescribing errors were defined in relation to the patient, chemotherapy regimen and hospital organisation. The relationship between these risk factors and observed medication errors or dose medication errors was assessed by univariate and multivariate logistic-regression analyses.

Results: Among the 17,150 chemotherapy prescriptions, 540 contained at least one error (3.15%). The following independent predictors of risk of medication errors were identified: patients with a body surface area >2 m^2 (odds ratio (OR): 1.3, 95% confidence interval (CI) 1.01–1.67, $p = 0.04$), protocols with more than three drugs (OR: 1.91, 95% CI 1.59–2.31, $p < 0.001$), protocols involving carboplatin (OR: 2.33, 95% CI 1.85–2.95, $p < 0.001$), protocols

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requiring at least one modification by the physician (OR: 1.32, 95% CI 1.09–1.61, $p = 0.005$), inpatient care (OR: 1.58, 95% CI 1.28–1.93, $p < 0.001$) and prescriptions by a resident physician (OR: 1.83, 95% CI 1.50–2.22, $p < 0.001$). The risk of medication dose prescribing errors was significantly associated with three independent factors: protocols involving carboplatin (OR: 4.47, 95% CI 3.45–5.79, $p < 0.001$), protocols with more than three drugs (OR: 2.4, 95% CI 1.92–3.00, $p < 0.001$) and protocols requiring at least one modification (OR: 1.33, 95% CI 1.04–1.69, $p = 0.02$).

Conclusion: In this epidemiologic study, the independent risk factors identified should be targeted for preventive measures in order to improve anticancer agent prescriptions and reduce the risk of medication errors.

1. Introduction

Although certain adverse drug events are inevitable, others caused by medication errors are preventable.[1] The high toxicity of antineoplastic drugs and their narrow therapeutic index along with the health status of cancer patients make prescribing errors potentially harmful. We previously reported that 5.2% of antineoplastic prescriptions contained at least one medication error, but that very few medication errors actually reached patients.[2] Nevertheless, when considering medication errors, antineoplastic drugs are the second most common cause of death.[3] Antineoplastic overdoses may result in permanent damage to patients, while underdoses may compromise the success of therapy. Overdose-related incidents have been mostly reported,[4–7] some of them being fatal.[8–11]

To enhance the safety of chemotherapy, the prevention of antineoplastic medication errors has become a priority in hospitals.[12] Numerous recommendations have been published in order to decrease the risk of errors.[13–15] However, the prescription phase is one of the most critical stages in terms of medication error risks, thereby making it an important target for improvement. Developing effective ways to reduce errors requires determining and understanding their causes in addition to the factors associated with them.

Our 2-year observational study thus aimed to identify the predictors of medication prescribing errors involving anticancer treatments, while considering patient-related factors, antineoplastic drugs and hospital organisation.

2. Methods

2.1. Settings

The study was conducted in a 1200-bed university hospital in France, which was largely involved in cancer patient care. In this centre, antineoplastic drugs were prescribed using standardised pre-printed forms based on the National Cancer Institute Thesaurus for all approved antineoplastic protocols. Physicians were required to approve the prescription by signature, thus authorising both cytotoxic drug preparation and administration if they regarded the clinical state of patients and their recent biological results to be adequate for treatment. The age, experience and status of prescribers varied, ranging from residents to senior attending physicians. Pharmacists were subsequently required to analyse prescriptions using dedicated pharmacy software (Asclepios®), in which patient data (identity, age, weight and height) as well as the intended antineoplastic regimen were entered. In addition, pharmacists were expected to investigate any dose adjustment or deviation from the validated antineoplastic regimen. All calculations, such as body surface area, dose capping with a maximum body surface area of 2 m^2, as well as day and duration of drug delivery, were automated.

2.2. Medication prescribing errors

All consecutive antineoplastic prescriptions from June 2006 to May 2008 were collected in a database. Prescriptions with medication errors, particularly dose errors, were included. Prescription errors were detected by pharmacists by means of a systematic pharmaceutical analysis of all prescribed antineoplastic regimens. Prescription errors were defined as failures in the treatment process, which led to or had the potential to lead to patient harm. These prescribing errors were classified, as described in Table 1. Dose errors were defined as an under- or overdose of more than 5% of antineoplastic drugs.

2.3. Potential risk factors

Three types of potential risk factors were identified:

- Patient-related factors: age ($\leqslant$75 years versus >75 years); body surface area ($\leqslant$2 m^2 versus >2 m^2) due to the dose capping to a maximum body surface area of 2 m^2 following the guidelines of our institution.
- Chemotherapy-related factors: prescriptions as part of a clinical trial; chemotherapy protocols including more than three injectable antineoplastic drugs; protocols requiring at least one modification to improve the efficacy or safety of drug administration (i.e. changes to the nature or volume of the solvent, modifications to the administration route, duration of administration or drug dose); protocols involving

Table 1
Classification of Medication Prescribing Errors.

Type of errors	Definition
Error linked to the choice of antineoplastic regimen	Differences in the antineoplastic regimen as compared to the previous cycle or the multidisciplinary medical decision
Dose error	Under- or overdose of more than 5% of antineoplastic drugs (i.e. calculation mistake, omission of dose reduction when a dosage adjustment was required)
Incomplete prescription	Data missing on the prescription, such as patient identity, anthropometric or biological data, drug dose, prescriber's signature and date of administration
Cancellation of medical approval	Misinterpretation of the clinical status of the patient, who was not able to receive chemotherapy

drugs with certain characteristics, such as a maximum capping dose (i.e. vincristine), cumulative maximum dose (i.e. anthracyclines), weight-based dose calculation (i.e. trastuzumab) or formula including biological and pharmacokinetic parameters (i.e. carboplatin).
– Hospital organisation-related factors: prescription day (weekdays from Monday to Thursday versus Friday); prescriptions during public holidays; experience of prescriber (resident versus senior physician); treatment setting (inpatient or day-care units); medical specialty of the unit (haematology, medical oncology, gastroenterology, pneumology, radiation therapy and head and neck).

2.4. Statistical analysis

The unit of analysis was the prescribing medication order containing at least one medication error. Statistical analysis was applied to all error types. Criteria relating to patients and protocols were separately tested in terms of dose prescribing errors. The analyses of the risk factors for prescription errors were performed in two steps. Firstly, univariate analysis was performed to assess the relationship between potential risk factors and observed medication errors (all errors and medication dose errors) using chi-square test with a two-sided alpha risk level of 0.05. All explanatory covariates that were significant in univariate analysis were integrated into multivariate analyses using a logistic regression model with the R® software. The odds ratio (OR) and 95% confidence interval (CI) were computed, with the final logistic model obtained using a backward selection. All tests were conducted using a two-sided alpha risk level of 0.05.

3. Results

3.1. Data collection

Between June 2006 and May 2008, our pharmacy unit received a total of 17,150 cancer chemotherapy prescriptions for 2423 patients. Overall, 44.4% of prescriptions ($n = 7614$) were requested by the haematology department, followed by the medical oncology (23.4%, $n = 4008$) and pneumology departments (19.5%, $n = 3346$). Treatments were more frequently prescribed in the day-care unit compared with the inpatient unit (57.3% versus 42.7%). Prescriptions of antineoplastic drugs were most frequently authorised by senior oncologists (56.1% versus 43.9% for residents), although residents were the main prescribers in the inpatient unit (64.9% of prescriptions, $p < 0.0001$).

Among the 17,150 antineoplastic prescriptions, 540 contained at least one prescription error (3.15%). Among the incorrect prescriptions, 59.3% related to doses ($n = 320$), 43% to incomplete prescriptions with missing data ($n = 232$), and 9.63% to the selection of the antineoplastic regimen ($n = 52$). Moreover, in 20 cases (3.7%), prescribers requested the drug preparation process to be stopped due to the patient's clinical situation despite initially signing the medical approval.

3.2. Univariate analysis

The results from the univariate analysis are summarised in Table 2. Ten potential risk factors for prescribing errors were identified as significant and selected for multivariate analyses: patients with a body surface area $>2\ m^2$ ($p = 0.005$), protocols including more than three injectable antineoplastic drugs ($p < 0.001$), protocols requiring at least one modification by the prescriber ($p = 0.03$), protocols involving carboplatin ($p < 0.001$), protocols with at least one drug requiring a maximum dose not to be exceeded during injection ($p < 0.001$) or with doses calculated according to weight ($p = 0.0015$), prescriptions from the gastroenterology ($p = 0.04$) or medical oncology departments ($p < 0.001$), prescriptions by a resident ($p < 0.001$) and conventional hospitalisation ($p < 0.001$).

In addition, criteria relating to patients and protocols were separately analysed in terms of dose medication errors. The following were identified as significant potential risk factors for dose prescribing errors: patients with body surface area $>2\ m^2$ ($p = 0.04$), protocols with more than three injectable antineoplastic drugs ($p = 0.001$), protocols requiring at least one modification by the prescriber ($p = 0.0015$), protocols involving carboplatin ($p < 0.001$), protocols with at least one drug requiring a maximum dose not to be exceeded during injection ($p < 0.001$) or with doses calculated according to the weight ($p = 0.03$) (Table 3).

3.3. Multivariate analyses

The following factors were found to be significant independent risk factors for prescribing errors based on multivariate analyses: patients with a body surface

Table 2
Univariate analysis of the potential risk factors for medication prescribing errors.

N (%)	Prescription with at least one error ($N = 540$)	Total number of prescriptions ($N = 17{,}150$)	*p*-Value
Potential risk factors related to patients			
Age (years)			0.8
⩽75	476 (3.1)	15,175 (88.5)	
>75	64 (3.2)	1975 (11.5)	
Body surface area (m^2)			0.005
⩽2	463 (3.0)	15,335 (89)	
>2	77 (4.2)	1815 (11)	
Potential risk factors related to chemotherapy regimens			
Protocol with			<0.001
More than 3 injectable antineoplastic drugs	263 (5.0)	5216 (30.4)	
⩽3 injectable antineoplastic drugs	277 (2.3)	11,934 (69.6)	
Prescription			0.79
Within a clinical trial	67 (3.1)	2188 (12.8)	
Not integrated into a clinical trial	474 (3.2)	14,964 (87.2)	
Protocol			<0.001
With a maximum drug dose by injection	164 (5.5)	2995 (17.5)	
Without maximum drug dose by injection	376 (2.7)	14,155 (82.5)	
Protocol			0.43
With a maximum drug cumulative dose	108 (3.4)	3208 (18.7)	
Without a maximum drug cumulative dose	432 (3.1)	13,942 (81.3)	
Protocol			<0.001
With carboplatin	94 (6.6)	1424 (8.3)	
Without carboplatin	446 (2.8)	15,726 (91.7)	
Protocol requiring			0.03
At least one modification by the physician	151 (3.7)	4111 (23.9)	
No modification	389 (2.9)	13,309 (76.1)	
Protocol			0.0015
With a drug dose calculation according to weight	4 (0.8)	525 (3.1)	
Without a drug dose calculation according to weight	536 (3.2)	16,625 (96.9)	
Potential risk factors related to the organisation			
Prescription			0.89
On school holidays	168 (3.18)	5291 (30.9)	
Not on school holidays	372 (3.14)	11,859 (69.1)	
Prescription			0.16
On Fridays	110 (2.8)	3918 (22.8)	
Not on Fridays	430 (3.2)	13,232 (77.2)	
Status of prescribers			<0.001
Resident	333 (4.4)	7525 (43.9)	
Senior	207 (2.2)	9625 (56.1)	
Medical specialties			
Haematology	259 (3.4)	7614 (44.4)	0.89
Medical oncology	92 (2.3)	4007 (23.4)	<0.001
Pneumology	115 (3.5)	3346 (19.5)	0.29
Radiation therapy	26 (2.7)	970 (5.7)	0.39
Gastroenterology	29 (4.5)	642 (3.7)	0.04
Head and neck cancer unit	11 (2.7)	405 (2.4)	0.61
Others	8 (4.8)	166 (0.9)	0.22
Type of hospitalisation			<0.001
Day care unit	197 (2.0)	9826 (57.3)	
Inpatient unit	343 (4.7)	7324 (42.7)	

area >2 m^2 (OR: 1.3, 95% CI 1.01–1.67, $p = 0.04$), protocols with more than three injectable antineoplastic drugs (OR: 1.91, 95% CI 1.59–2.31, $p < 0.001$), protocols requiring at least one modification by the physician (OR: 1.32, 95% CI 1.09–1.61, $p = 0.005$), protocols involving carboplatin (OR: 2.33, 95% CI 1.85–2.95, $p < 0.001$), inpatient care (OR: 1.58, 95% CI 1.28–1.93, $p < 0.001$) and prescription by a resident (OR: 1.83, 95% CI 1.5–2.22, $p < 0.001$). Prescriptions from the medical oncology department were more favourable in terms of the risk of antineoplastic prescribing errors when compared to prescriptions from other departments

Table 3
Univariate analysis of the potential risk factors for dose errors.

N (%)	Prescription with at least one dose error ($N = 320$)	Total number of prescriptions ($N = 17{,}150$)	*p*-Value
Potential risk factors related to patients			
Age (years)			0.98
⩽75	283 (1.9)	15,175 (88.5)	
>75	37 (1.9)	1975 (11.5)	
Body surface area (m^2)			0.04
⩽2	275 (1.8)	15,335 (89.4)	
>2	45 (2.5)	1815 (10.6)	
Potential risk factors related to chemotherapy regimens			
Protocol with			<0.001
More than 3 injectable antineoplastic drugs	157 (3)	5216 (30.4)	
⩽3 injectable antineoplastic drugs	163 (1.4)	11,934 (69.6)	
Prescription			0.84
Within a clinical trial	42 (1.9)	2188 (12.8)	
Not integrated into a clinical trial	278 (1.9)	14,964 (87.2)	
Protocol			<0.001
With a maximum drug dose by injection	120 (4)	2995 (17.5)	
Without maximum drug dose by injection	200 (1.4)	14,155 (82.5)	
Protocol			0.46
With a maximum drug cumulative dose	65 (2)	3208 (18.7)	
Without a maximum drug cumulative dose	255 (1.8)	13,942 (81.3)	
Protocol			<0.001
With carboplatin	83 (5.8)	1424 (8.3)	
Without carboplatin	237 (1.5)	15,726 (91.7)	
Protocol requiring			0.0015
At least one modification by the physician	97 (2.4)	4111 (23.9)	
No modification	223 (1.7)	13,309 (76.1)	
Protocol			0.03
With a drug dose calculation according to weight	3 (0.6)	525 (3.1)	
Without a drug dose calculation according to weight	317 (1.9)	16,625 (96.9)	

(OR: 0.65, 95% CI 0.52–0.83, $p < 0.001$). Protocols involving drugs with a capping dose or weight-based dose calculation were not predictors of errors (Table 4).

Multivariate analyses on dose prescribing errors resulted in the identification of three significant risk factors: protocols with more than three injectable antineoplastic drugs (OR: 2.4, 95% CI 1.92–3.0, $p < 0.001$), protocols requiring at least one modification by the prescriber (OR: 1.33, 95% CI 1.04–1.69, $p = 0.02$) and protocols involving carboplatin (OR: 4.47, 95% CI 3.45–5.79, $p < 0.001$) (Table 5).

4. Discussion

In our study, antineoplastic medication errors occurred at a non-negligible rate of 3.15%, which was consistent with the rates reported in the literature ranging from 0.4% to 31.9%.[2,16–18] Outcomes in these studies largely depended on study design and the definition of medication error.

Six risk factors were identified as predictors of oncology medication errors based on 17,150 prescriptions. Patients with body surface area >2 m^2 were found to be at greater risk of prescribing errors due to the dose capping. Dose limitations based on body surface area are historic, but usually performed.[19] Risk factors related to chemotherapy regimens were also identified. In particular, protocols involving more than three antineoplastic drugs were associated with a higher risk of prescribing errors, which may be easily explained on account of the multiple dose calculations required. This outcome was reported by other authors based on analyses of handwritten[20] or computerised prescriptions.[21] Moreover, doses adjustments, mostly reductions on account of toxicity, were frequently overlooked during subsequent cycles. This type of error involving an inaccurate adjustment was previously reported in 43.1% of antineoplastic drug dose errors when a computerised system was used.[21]

In our study, risk factors related to hospital organisation were analysed. Inpatient care appeared to be at a higher risk of prescribing errors compared with daycare. This result was unexpected, since there were fewer chemotherapy prescriptions in inpatient care units than daycare units. Possible explanations may include the multiple unscheduled tasks performed in inpatient units, the more complex antineoplastic regimens prescribed, as well as the fact that residents were the main prescribers

Table 4
Results from the multivariate analysis of medication prescribing errors.

Risk factors for prescribing errors	Odds ratio	95% confidence interval	*p*-Value
Potential risk factors related to patients			
Body surface area >2 m^2	1.30	[1.01; 1.67]	0.04
Potential risk factors related to chemotherapy regimens			
Protocol with more than 3 injectable antineoplastic drugs	1.91	[1.59; 2.31]	<0.001
Protocol with carboplatin	2.33	[1.85; 2.95]	<0.001
Protocol requiring at least one modification by the physician	1.32	[1.09; 1,61]	0.005
Potential risk factors related to the organisation			
Prescription by residents	1.83	[1.50; 2.22]	<0.001
Medical oncology ward	0.65	[0.52; 0.83]	<0.001
Inpatient unit	1.58	[1.28; 1.93]	<0.001

Table 5
Multivariate analysis of risk factors for dose errors.

Risk factors of dose errors	Odds ratio	95% confidence interval	*p*-Value
Protocol with more than 3 injectable antineoplastic drugs	2.40	[1.92; 3.00]	<0.001
Protocol with carboplatin	4.47	[3.45; 5.79]	<0.001
Protocol requiring at least one modification by the physician	1.33	[1.04; 1,69]	0.02

in inpatient units. Indeed, clinical experience was found to have an important impact on the risk of prescribing errors. The prescription of antineoplastic drugs by residents was a detrimental risk factor for prescribing errors, as was similarly reported by Nerich et al.[21] This observation highlights the relevance of senior supervision throughout the prescription process, which should take into account all prescribing risk factors, such as the complexity of the patient, competence of the resident, medications being prescribed and availability of guidelines.[22] It would be interesting to investigate if these errors were related to the prescriber's lack of training or experience.[23] Finally, Zaal et al. reported that medication orders prescribed on Fridays or Saturdays had a higher risk of medication errors,[24] although this was not a significant factor in our study, especially given that fewer cancer treatments were initiated over the weekend.

On account of the frequency and severity of dose errors, we performed a subanalysis of these errors given that 59.3% of our erroneous protocols included at least one wrong dose. Fijn et al., for example, identified cancer therapy as a predictor of dosing errors.[25] Our percentage of dose errors was higher than that reported in the literature, even though the dose errors were the predominant source of prescribing errors.[26,27] Three risk factors of dose prescribing errors were identified in our analysis. The dose errors in protocols involving carboplatin could be explained by the unusual and complex dose calculation of this agent, which is based on several parameters, including biological and pharmacokinetic values. In our hospital, either the Chatelut formula or Calvert formula was used at the discretion of the prescriber, which may have been a source of confusion. Greater training of residents in errors as well as calculating carboplatin dosage should be considered by their supervisors. Prescriptions by residents and protocols with more than two antineoplastic drugs were identified as risk factors in previous studies,[21] similar to our own.

Further studies on the factors influencing medication errors are still necessary, but they can be viewed from two perspectives: the person approach and the system approach.[28] Errors due to memory lapses or attention slips, errors of judgment and errors caused by a lack of knowledge need to be distinguished so that corrective steps can be launched.[29] Moreover, the system approach must be strengthened, focusing on the work conditions of individuals and trying to build defences to avoid errors or mitigate their effects.

The results of our study need to be viewed within their limited context. The study was conducted in a single university hospital. Computerised prescriptions, the prescription of antineoplastic drugs by residents without supervision, in addition to the role of pharmacists are important organisational differences, which need to be taken into account. Patients with a body surface area >2 m^2 may not be at a higher risk of medication errors, since the maximum body surface area of 2 m^2 is not applied in all cancer centres. Another limitation of our study was that oral antineoplastic chemotherapy was not assessed. Finally, as only intercepted prescription errors were analysed, the findings cannot be regarded as complete.

5. Conclusion

This study demonstrated that predicting the risk of antineoplastic medication errors is feasible and may be useful to help improve quality by targeting the identified

risk factors with preventive measures. Such an approach would allow for more informed interventions in order to improve quality and safety. For each medication error, organisational and human factors should be identified by the medical and pharmaceutical staff so as to limit its recurrence. This multidisciplinary work is necessary if we are to learn from our mistakes so that medication errors can be reduced and quality of care improved.

Moreover, the prediction of individual patient outcomes may be of particular value during hospitalisation. Risk adjustment models were previously developed to predict hospital mortality following surgery and anaesthesia.[30,31] Such a model should be developed in oncology in order to predict the individual patient risk prior to antineoplastic treatment, thus allowing medical, nursing and pharmaceutical teams to increase their vigilance for high-risk patients.

Conflict of interest statement

None declared. No direct funding was received for this study. The authors were personally salaried by their institutions during the period of writing (though no specific salary was set aside or given for the writing of this paper).

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