

Chemotherapy Dose Limits Set by Users of a Computer Order Entry System

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Abstract

Objective: The elimination of dosing errors related to chemotherapy administration remains an elusive goal. Computerized order entry reduces errors but is not widely used. One problem in implementing computer dose checking is the lack of standardized dose limits. We evaluated the dose limits set for chemotherapeutic agents by users of a computer order entry system.

Methods: Oncology practices from 82 sites using a computer order entry system submitted data via the Web to a central data warehouse on 280,047 drug administrations for 16,976 patients. Data were blinded to patient and site but included the diagnosis, age, chemotherapy regimens, dosages, and dose adjustments. Dose limits, set by users at each location, were assessed. For commonly used regimens, the range of customary doses was also assessed.

Results: The mean dose limit was less than that for a body surface area (BSA) of 2.2 meter squared in 43/44 (98%) of the drugs dosed according to BSA. This user set dose limit was exceeded in only 3% of drug administrations.

Conclusion: In setting computerized dose limits, most oncologists use a dose limit below that for a BSA of 2.2 meters squared. This user set limiting dose was rarely exceeded, with 97% of dosages below the limits set in this computer order entry system.

Keywords — chemotherapy dose safety; computerized order entry

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Complications of drug use were the most frequent subtype of adverse events noted in the Medical Practice Study, which evaluated the risk of iatrogenic injury in 30,000 patients discharged from acute care hospitals in 1984.² Medication errors accounted for 19% of all adverse events identified.

A wide variety of preventive measures have been suggested to prevent chemotherapy mishaps. These include standardized order forms, manual and computerized pharmacy review of orders, and attending co-signature for chemotherapeutic agents.^{3,4,5} Of these methods, only computerized order entry has been formally evaluated and shown to reduce errors.⁶ Unfortunately, lethal errors continue to be reported,⁷ and computerized order entry has not been widely adopted.⁸

One of the problems encountered in establishing computerized safeguards for chemotherapy dosing is the difficulty in establishing a maximum dose for any given agent. Dosages vary according to each chemotherapy regimen, which have unique dose-limiting toxicities that are evaluated during phase 1 trials. In addition, specialized units using bone marrow rescue routinely use drug dosages that would be lethal without rescue. Based on these issues, it is difficult to set a single maximum dose for any given drug in a computer system that monitors

Over the past decade, several lethal errors in chemotherapy administration have received national attention. With increased public and professional scrutiny, it has been recognized that medication errors are not rare. The Institute for Safe

Medication Practices (ISMP), through voluntary and anonymous reports, compiled 1,385 cases of medication errors nationwide between 1991 and 1994.¹ Chemotherapeutic agents were involved in 24 cases; in seven mishaps, the errors were fatal.

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Figure 1. Error message produced by IntelliDose when limiting dose is exceeded.

user—if appropriate privileges are granted by the system administrator (see Figure 1). All dose calculations, including BSA, area under the curve (AUC), and estimation of creatinine clearance (CrCl) are done by computer.

For the most commonly used chemotherapy regimens, the means of the drug dose administered, dosage adjustments, and limiting dose were calculated. The number of cases where the dose exceeded the limiting dose was recorded for each regimen.

RESULTS

Demographic information for the 10 most common diagnoses is listed in Table 1. The range of patient’s ages was 8 months to 102 years, with a mean of 59. The mean patient’s weight was 76 kg, with a range of 5 to 245 kg. The mean age and weight of male and female patients according to diagnosis are listed for the 10 most common diagnoses.

The customary doses and mean limiting dose of the 25 most commonly used chemotherapy regimens are listed in Table 2. For drug dosages calculated by BSA, the mean dose was always less than the value for a BSA of 2, but the upper range of doses frequently exceeded this limit.

The mean limiting dose was close to the value for a BSA of 2 in all drugs dosed according to BSA. The only exception was for cyclophosphamide 100 mg/m² in the cyclophosphamide/methotrexate/fluorouracil (CMF) regimen, where the mean limiting dose was 263 mg/m². In every other instance, the mean limiting dose was less than that for a BSA of 2.2.

Dose adjustments are shown in Table 3. There was substantial variation in the mean dose adjustment according to regimen, with a

chemotherapy dosing.

In this study, we evaluated the range of chemotherapy dosages that are used for the most commonly administered regimens, as well as, the limiting dose set by the users of a computerized order entry system. Our goal was to identify practical standards for limiting doses of chemotherapeutic agents.

MATERIAL AND METHODS

After obtaining institutional review board approval from the University of Rochester School of Medicine, a centralized data warehouse was accessed to obtain information regarding the diagnosis and treatment of 16,976 patients from 82 sites nationwide. Information on 280,047 chemotherapy drug administrations during 2003 was obtained, which included the patient’s diagnosis, age, chemotherapy regimen, dosages, and dose adjustments. The specialty of the provider (medical, gynecologic, or pediatric

oncology) was noted, but no information that would uniquely identify the patient, practitioner, or institution was collected. The data warehouse was kept in a central, password protected SQL Server (Microsoft Corp., Redmond, Washington) database, which was updated automatically by the periodic transmission of data via the web from each location.

The computer order entry system used at each location, *IntelliDose* (IntrinsiQ Research, Waltham, Massachusetts), was developed for oncology and includes a variety of dose-checking algorithms. The software requires setting a limiting dose for each chemotherapeutic agent in a given regimen. The software suggests setting a limiting dose based on a body surface area (BSA) of 2 meters squared, but does allow the users to set a higher-limiting dose. Warning messages are given at the time of order entry, if the limiting dose is exceeded. The limiting dose can be overridden by the

Table 1. Demographic Characteristics of Cancer Patients

<i>Most Common Cancer Diagnoses (Top 10)</i>	<i>Mean Age (yrs)</i>	<i>SD</i>	<i>Mean Weight (kg)</i>	<i>SD</i>
Males				
Lung (non-small cell)	66	11	80	17
Lung (small cell)	65	10	82	19
Colon	66	12	87	19
Lymphoma (Hodgkins)	47	18	84	22
Lymphoma (non-Hodgkins)	63	15	87	17
Esophageal	65	11	88	24
Leukemia (chronic lymphocytic)	67	11	85	16
Pediatric	13	9	41	25
Rectal	64	11	82	17
Head/neck	59	11	78	18
Females				
Breast	57	13	78	18
Lung (non-small cell)	66	11	67	17
Lung (small cell)	65	10	99	16
Ovary	63	13	73	19
Colon	62	13	71	19
Lymphoma (Hodgkins)	46	18	70	18
Lymphoma (non-Hodgkins)	66	16	71	18
Pediatric	14	16	35	25
Uterine	66	11	77	22
Rectal	63	13	69	16

SD = standard deviation

resulted in a 55% reduction in serious medication errors.⁶ Unfortunately, hospital-wide CPOE systems have not been widely adopted and are not suitable for most office-based oncologists.⁸ Moreover, a recent survey suggests that the majority of current hospital and/or pharmacy computer systems are unlikely to provide even rudimentary safety checking.¹⁰ In order for hospital or pharmacy computer systems to provide safety checking of dosages, standardization of limiting doses will be required.

IntelliDose software was designed specifically for oncology practices and incorporates a variety of error checking routines for drug dosage. Single, multiple, and cumulative doses are monitored for all drugs and are checked against user set limits. Since calculations related to chemotherapy dosing are done by the computer, it should be possible to eliminate arithmetic errors. In our preliminary experience, use of the software eliminated prescribing errors in chemotherapy dosing.¹¹ In no instance was a drug dose miscalculated, misinterpreted, or set beyond the chosen safety limits. However, these results were based on a single practice and may not reflect how the software is used in other sites. Limiting doses and the rights to override doses were set independently by the system administrator at each site.

In this study, we evaluated the customary doses and user set dose limits for frequently used chemotherapy regimens from a large number of oncology practices. As would be expected, there was substantial variation in drug dosages. For example, in the regimen carboplatin AUC = 6/paclitaxel 175 mg/m² (see Table 2), the range of carboplatin dosing was

mean 20% reduction in dose for irinotecan (125 mg/m²) and a mean 7% increase in dose for topotecan (1.5 mg/m²). Capecitabine (1,250 mg/m²) had the most frequent dose adjustments, with only 23% of administrations given without a dose adjustment.

DISCUSSION

The elimination of chemotherapy dosage errors, at least those related to prescribing, should be achievable through the use of computer technology. However, chemotherapy dosing is complex, very individualized, and there are no published standards regarding

limiting doses of the agents used in the multitude of current chemotherapy regimens. Numerous suggestions have been made to reduce or eliminate chemotherapeutic dosing errors. The Institute for Safe Medication Practices (ISMP) has recommended standardized order forms, pharmacy recalculation of all dosing, and computer checking of maximum doses.³ The Institute for Healthcare Improvement has also called for establishing dose limits for chemotherapy agents.⁹

Bates et al recently reported that computerized physician order entry (CPOE) in a hospital setting

Table 2. Customary Chemotherapy Dosages and Limiting Dose

<i>Regimen</i>	<i>Dose Basis*</i>	<i>Mean Dose</i>	<i>SD</i>	<i>Range</i>	<i>Mean Limiting Dose</i>	<i>SD</i>
Single Agents						
Capecitabine	1,250	1,822	570	500 to 3,800	2,547	314
Docetaxel	35	60	11	27 to 203	74	10
Gemcitabine	1,000	1,627	361	50 to 2,935	2,043	147
Fluorouracil	500	834	165	100 to 1,350	1,054	114
Fludarabine	25	46	8	20 to 69	52	4
Irinotecan	125	180	60	25 to 530	264	21
Paclitaxel	80	138	23	73 to 278	164	16
Rituximab	375	701	111	100 to 1,100	765	37
Topotecan	1.5	2.9	1.6	1 to 9	3	0.5
Trastuzumab	2 mg/kg	160 mg	62	60 to 523 mg	156 mg	36
Vinorelbine	30	47	10	13 to 86	62	6
Combination Regimens						
Capecitabine/ oxaliplatin	1,000 130	1,650 225	372 45	500 to 2,652 94 to 322	2,072 257	286 35
Carboplatin/ paclitaxel	6 † 175	578 302	168 46	101 to 1,465 80 to 493	760 354	115 20
Carboplatin/ paclitaxel	2 † 80	198 136	62 27	50 to 1,030 47 to 200	256 164	103 16
Carboplatin/ etoposide	6 † 100	540 171	169 32	100 to 1,252 27 to 341	740 207	90 17
Carboplatin/ gemcitabine	5 † 1,000	455 1,671	143 357	100 to 1,341 320 to 2,763	646 2,010	86 134
Cytosxan/ methotrexate/ fluorouracil	100 40 600	193 67 1,006	135 12 162	63 to 1000 26 to 95 378 to 1,428	263 82 1,231	295 5 70
Cytosxan/ Doxorubicin	600 60	1,070 106	118 12	490 to 1,520 33 to 150	1,245 124	85 9
Docetaxel/ estramustine	35 280 (dose)**	65 273	12 30	30 to 83 140 to 280	72 280	4 0
Fluorouracil/ irinotecan	500 125	859 206	178 46	250 to 1,440 50 to 303	1,027 257	73 17
Fluorouracil/ oxaliplatin	400 85	708 150	135 29	200 to 1,070 47 to 238	829 175	68 11
Mercaptopurine/ methotrexate/ vincristine	75 20 1.5	121 33 2.4	34 9 0.7	48 to 160 13 to 44 1 to 3	125 34 2	44 12 0.1
Cyclophosphamide/ cytarabine/ doxorubicin/ mercaptopurine/ methotrexate/ pegaspargase/ thioguanine/ vincristine	1,000 75 25 75 20 2,500 60 1.5	829 62 19 73 19 2,157 47 1.3	217 17 4 30 8 849 9 0.5	593 to 1,440 41 to 108 15 to 29 43 to 149 11 to 40 1480 to 5,000 33 to 70 0.9 to 3	1,059 81 25 65 19 5,000 60 2.1	243 20 0 30 9 0 0 0.3
Cyclophosphamide/ doxorubicin/ rituximab/ vincristine	750 50 375 1.4	1,355 90 700 2	227 15 87 0.2	340 to 2,288 25 to 130 250 to 976 1 to 3	1,550 103 774 2.1	107 7 54 0.3
Cyclophosphamide/ doxorubicin/ paclitaxel	600 60 175	1,070 106 308	118 12 34	490 to 1,520 33 to 150 120 to 420	1,236 123 364	89 10 34

*All values for dose basis in mg/m² unless otherwise specified**No calculation is made for dose; all patients receive 280 mg

†Carboplatin dosing according to area under the curve SD = standard deviation

Table 3. Chemotherapy Regimen Dose Adjustments

<i>Regimen</i>	<i>Dose Basis#</i>	<i>Mean Dose Adjustment (%)</i>	<i>No Dose Adjustment (%)</i>	<i>Administrations Exceeding Limiting Dose (%)</i>
Single Agents				
Capecitabine	1,250	-18	23	0.2
Docetaxel	35	-5	72	0.9
Gemcitabine	1,000	-9	63	1.4
Fluorouracil	500	-9	54	1.4
Fludarabine	25	-4	74	0.8
Irinotecan	125	-20	32	1.5
Paclitaxel	80	-3	75	2
Rituximab	375	-1	90	4.3
Topotecan	1.5	7	37	2.5
Trastuzumab	2 mg/kg	7	93	6.1
Vinorelbine	30	-11	53	0.7
Combination Regimens				
Capecitabine/ oxaliplatin	1,000 130	-9 -8	60 67	0.3 10.6
Carboplatin/ paclitaxel	6* 175	-4 -3	74 85	1 4.1
Carboplatin/ paclitaxel	2* 80	-2 -5	84 77	5.4 2.4
Carboplatin/ etoposide	6* 100	-8 -5	59 69	8.3 2.1
Carboplatin/ gemcitabine	5* 1,000	-6 -8	71 63	6.8 3.9
Cyclophosphamide/ methotrexate/ fluorouracil	100 40 600	7 -5 -5	65 77 77	0.5 1.2 1.8
Cyclophosphamide/ doxorubicin	600 60	-1 -1	89 89	2.4 2.1
Docetaxel/ estramustine	35 280 (dose)	-5 -2	61 95	3.7
Fluorouracil/ irinotecan	500 125	-8 -12	61 48	1.9 1.3
Fluorouracil/ oxaliplatin	400 85	-6 -6	74 68	2.4 3.8
Mercaptopurine/ methotrexate/ vincristine	75 20 1.5	0 0 0	94 100 100	0.8 5.7 21.3
Cyclophosphamide/ cytarabine/ doxorubicin/ mercaptopurine/ methotrexate	1,000 75 25 75 20	0 0 0 0 0	100 100 100 100 100	11.8 1.3 4.5 1.1 10
pegaspargase/ thioguanine/ vincristine	2,500 60 1.5	0 0 0	100 100 100	0 0.8 3
Cyclophosphamide/ doxorubicin/ rituximab/ vincristine	750 50 375 1.4	-3 -3 0 -5	80 82 91 84	5.8 4.4 5.7 0.3
Cyclophosphamide/ doxorubicin/ paclitaxel	600 60 175	-1 -1 -1	92 92 92	2.1 1.7 2.9

All values in mg/m² unless otherwise specified
 *Carboplatin dosing according to area under the curve
 SD = standard deviation

101 to 1,465 mg, and the range of *Taxol* dosing was 80 to 493 mg. Given this wide range of drug dosages, it might at first appear difficult to establish practical standards for a limiting dose. At what dose level should a warning be given? Can a limit be established that should never be overridden by the user of these systems?

Despite the wide range of dosages, there seemed to be some consensus among practitioners regarding limiting doses. Again, using the carboplatin/*Taxol* regimen as an example, the mean limiting dose for carboplatin was 760 mg, and for *Taxol* it was 354 mg. In both cases, the standard deviation was within 15% of these values, reflecting the narrow range in limiting dose set by users of this system. In addition, it was unusual for these limiting doses to be overridden. As shown in Table 3, users exceeded the limiting dose in only 1% of carboplatin administrations and in only 4% of *Taxol* administrations. Unfortunately, we do not have any data about why user-set limiting doses were overridden; although, in some cases it appears that the limiting dose set by the user was lower than the mean for the group.

The mean limiting dose, which was derived from the 82 sites that submitted data, provides some guidance toward establishing a standard upper limit for drug dosing. Using a dose limit based on a BSA of 2.2 seems practical, as it was unusual for this dose level to be exceeded, and virtually all the mean dose limits were set below this level. However, this may be too restrictive in some circumstances, especially with an increasingly obese population. Obese patients may have dosages reduced by the use of ideal body weight or other types of dose-limiting

schemes.¹² This practice may result in suboptimal treatment, and is not supported by available data.¹³ In the computer order entry system in use at Strong Memorial Hospital, the Cancer Center pharmacy has set an upper limit BSA of 2.5. However, even this is a relative limit, and may be exceeded following discussion of the case with a cancer center pharmacist.

Despite heightened public and professional awareness, lethal errors in prescribing of chemotherapeutic agents continue to occur. In a well-known case,⁷ a decimal point error led to a lethal cisplatin overdose in an infant, when an order for cisplatin 20.4 mg was misinterpreted as 204 mg. In another more recent case, a 41-year-old man in California received 500 mg of cisplatin rather than 50 mg.¹⁴ The error was attributed to misinterpretation of a hand-written prescription. These types of events, although infrequent, should provide the impetus for more widespread adoption of computer order entry systems, especially for chemotherapeutic agents.

Setting dosage limits for computerized checking is complicated by the wide range of chemotherapy dosages and the numerous regimens used. Despite the complexity of chemotherapy dosing, use of computer technology should allow the elimination of arithmetic errors, decimal point errors, and errors related to poor handwriting.¹⁵ We hope that by providing these data on dose limits from a large number of oncology practices that it will be possible to develop practical standards for computerized dose checking of chemotherapeutic agents.

FINANCIAL DISCLOSURE

Dr. DuBeshter holds stock in

IntrinsiQ Research, the company that markets *IntelliDose* software. The other authors have no disclosures to report.

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