■ Article

Development of a Policy and Procedure for Accidental Chemotherapy Overdose

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A policy regarding rapid response to chemotherapy overdoses was developed by the authors in an attempt to minimize morbidity and mortality. The parameters of a chemotherapy overdose were defined to promote early recognition of an overdose incident. Resources needed to guide potential therapeutic interventions and required monitoring were developed. The policy defines the immediate actions to be taken in the event of a chemotherapy overdose. The availability of a chemotherapy overdose policy provides an enhanced level of safety for patients by ensuring that appropriate treatment is initiated without delay. The development of the policy was in response to the reporting of a tragic error at another institution. Healthcare providers must recognize and address potential areas of vulnerability to maximize patient safety.

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Chemotherapy protocols are complex and often administered in busy environments under temporal constraints. Enormous effort has been devoted to prevent chemotherapy error with attention focused on computer physician order entry, improved infusion pump technology, advanced IV workflow systems, specialty credentialing, and multiple double checks (Fischer, Alfano, Knobf, Donovan, & Beaulieu, 1996; Goodin et al., 2011; Institute of Medicine, 2000). Despite these preventive measures, erroneous chemotherapy administration can still occur, with potentially tragic consequences in the case of an overdose. The publication of a root cause analysis of a fatal fluorouracil overdose in Canada (Institute for Safe Medical Practices [ISMP], 2007) identified multiple causative factors; chief among them was the lack of a coordinated, rapid response to the overdose resulting from the absence of a defined treatment protocol for accidental chemotherapy overdose. According to the report, "Staff members were uncertain as to how best to treat and support the patient after the overdose was detected" (p. 6). This published root cause analysis prompted the Yale-New Haven Hospital chemotherapy safety committee, comprised of oncologists, oncology nurses, and oncology pharmacists, to reassess the processes to ensure a robust response to any chemotherapy overdose. This article describes the policy and procedure developed by the authors to ensure rapid response to accidental administration of an overdose of a chemotherapeutic drug (Moore, Grasso, Barbarotta, Nelson, & Fischer, 2009).

Definition of Chemotherapy Overdose

Fundamental to establishing a response protocol to chemotherapy overdose was to define chemotherapy overdose. A universal definition of overdose is complicated by the large number and diverse therapeutic indices of chemotherapeutic agents used in oncology and by a paucity of clinical literature on this topic. In addition, the route of administration, pharmacokinetics, and toxicity profile of the overdosed chemotherapeutic drug also would influence the specific response that medical personnel should make. Key clinical parameters of the patient also would affect the outcome, including performance status, age, and comorbid conditions. That multifactorial complexity led the authors to establish a conservative, broad definition

of potential overdose that encompasses relatively minor variances as well as egregious overdose events. Because of a lack of literature, the criteria to define a chemotherapy variance with potential for overdose was determined by the authors with approval from the medical director of the oncology program (see Figure 1). Even minor chemotherapy variances may indicate a need for improved processes. Identification and correction of these irregularities and their causes should decrease the chance of serious variance or overdose. The authors' primary objectives in the codification of chemotherapy overdose policy were to increase the vigilance of error identification and to provide guidelines for appropriate responses to overdose events. The policy and procedure divides the process of response to an identified variance in chemotherapeutic drug administration into eight components: notification and information access, patient assessment, treatment plan and intervention, monitoring and reassessment, documentation, patient and family education, staff education, and variance analysis.

Notification and Information Access

Activating a defined notification algorithm is a critical element of a rapid response to a chemotherapy variance (Institute of Medicine, 2000). The error may be discovered by any member of the oncology treatment team, the patient, or the patient's family or significant other. The patient may be in the hospital, outpatient setting, or at home when an error is discovered. Notification of the patient and family is the responsibility of the attending oncologist. Of utmost importance is that the patient be evaluated as soon as possible by the attending oncologist. A patient's nurse may be the one to discover the error, but this may not be true in every case. If the patient is in the hospital, the nurse caring for the patient must be immediately notified at the time the error is discovered. For patients at home, initial actions should be directed by the oncologist via phone communication. The authors' communication algorithm was designed to immediately notify experienced personnel, escalating the decision making toward the attending physician with additional help from the medical director of the oncology program and knowledgeable oncology nursing and pharmacy staff. This team of senior staff adds objectivity, expertise, and accountability to the patient assessment process (Katzenbach & Smith, 1994) (see Figure 2). The core group, comprised of the attending oncologist, clinical nurse specialist, and oncology pharmacy specialist, will promptly assess the patient, review the institutional chemotherapy overdose protocol, obtain literature, and contact appropriate consultation services to determine the best course of action. If not an inpatient, admission to the hospital is at the discretion of the attending oncologist and the medical director of the oncology program. If the variance involves an investigational new drug or a clinical trial, the institutional principal investigator and institutional review board must be promptly notified. Accountability is ensured through the immediate notification of the medical director of the oncology program, the director of nursing, and notification of the legal and risk services departments.

To rapidly access pertinent information related to chemotherapy variance, the policy and procedure provides instructions about how to quickly navigate the relevant online resources to find drug-specific toxicology and emergency management information. The authors' institution uses online versions of MicroMedex® and Poisindex®, which are available at all hospital clinical workstations and through employee home access. The policy and procedures also provide contact information for the state poison control center.

Patient Assessment

Prompt patient assessment by the attending physician or his or her clinical representative (nurse practitioner or physician assistant) is a critical early step. A main premise is that most, if not all side effects will be increased in a significant chemotherapy variance or overdose situation. A broad baseline of laboratory and metabolic values documenting bone marrow, renal, and hepatic function should be established. Key diagnostic actions include

- Physical examination and vital signs, paying particular attention to signs and symptoms of infection and drug toxicity
- Complete blood count with differential; comprehensive metabolic panel including electrolytes, calcium, magnesium and phosphate; blood urea nitrogen; serum creatinine; liver function tests; and coagulation parameters (prothrombin time, partial thromboplastin time)
- If the patient is symptomatic, obtain a chest x-ray; blood, urine and sputum cultures; and administer broad spectrum antibiotics per institutional guidelines.

Medical personnel should contact appropriate consultation services. The exception is a mandatory, immediate consultation with neurology and neurosurgery in the event of an intrathecal overdose (see Figure 3).

Treatment Plan and Intervention

Time is a critical factor in a potential overdose situation. Prompt response can have a significant impact on patient outcome (Goldfrank, 2006). In addition to notifying all personnel listed on the notification algorithm, the oncology treatment team may contact the state poison control center to obtain additional information. Initial general interventions should include establishing IV access and beginning hydration and forced diuresis, if not contraindicated. After consulting current pharmacology and toxicology references, the oncology team should create a list of possible side effects and initiate specific prophylaxis measures based on involved systems (see Table 1).

- Chemotherapy dose administered is more than 10% larger than prescribed.
- Chemotherapy dose was administered at a rate more than 25% faster or slower than prescribed.
- Chemotherapy dosage interval of administration was significantly shorter than prescribed. Variable was based on pharmacokinetics of the specific drug.
- The chemotherapy administered was contraindicated because of a patient's organ system dysfunction (i.e., failure to appropriately dose reduce).
- Administration of rescue medication, such as leucovorin following methotrexate, was omitted or delayed.

FIGURE 1. Chemotherapy Variance Requiring Evaluation

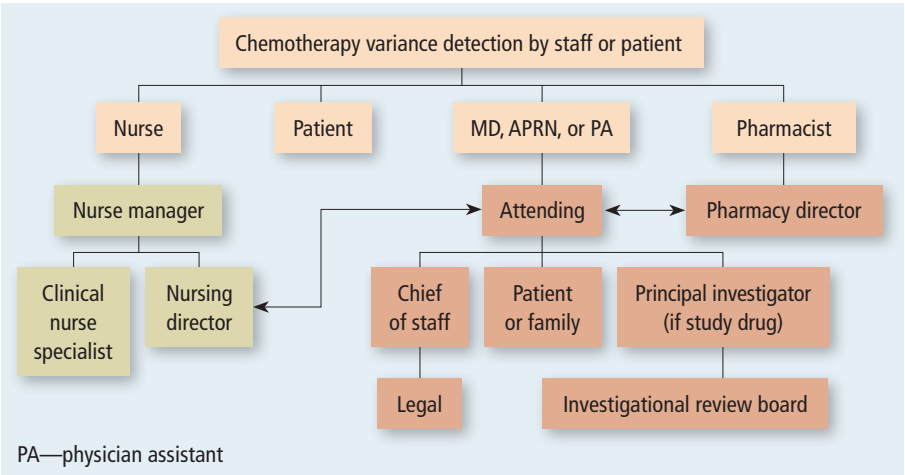

FIGURE 2. Notification Algorithm for Chemotherapy Overdose

At this time, appropriate consultation services should be contacted. The oncology pharmacist should review the complete list of medications the patient is taking, as drug interactions may affect the pharmacokinetics of the chemotherapy drug.

No known antidotes or reversal agents exist for many chemotherapy agents (Goldfrank, 2006; Goodin et al., 2011). As part of this policy, the authors compiled a table of therapeutic agents reported in the medical literature as possible interventions in the event of a chemotherapy overdose (see Table 2). The amount of supporting clinical data for overdose of the agents varied because of limited evidence and reliance on case reports. Attending oncologists should review the primary literature and make assessments based on the strength of evidence. If indicated, they should obtain and administer an intervention agent to minimize toxicity.

The potential for error increases with the rising number of oral chemotherapy agents prescribed and administered outside the supervision of a clinical setting. Elapsed time between ingestion and intervention is always a factor in successful management of overdose situations (Goldfrank, 2006), particularly for orally administered chemotherapeutic agents. However, an error may not be discovered immediately. Specific time-sensitive recommendations include the use of gastric lavage with airway protection if performed within one hour of ingestion (Goldfrank, 2006). Consider using activated charcoal with dose based on age.

Monitoring and Reassessment

Periodic monitoring and reassessment are critical as the status of the patient changes over time. Monitor all body systems as required, depending on the major toxicities of the agent(s) involved. Compare baseline laboratory values and review systems at regular intervals. Specifics of timing and laboratory parameters monitored will depend on the toxicity profile of the chemotherapy agent(s) involved and the route of administration. In addition, monitor parameters linked to specific interventions. Check for signs and symptoms of infection at regular intervals, assessing for expected toxicities and revisiting the need for subspecialty consults. The attending oncologist or clinical representative (nurse practitioner or physician assistant) should call and assess at-home patients daily or as often as clinically indicated.

Documentation

Clear and objective documentation is an essential aspect of this process. Personnel directly involved in a chemotherapy variance must complete an online medication event report. For a chemotherapy error, multiple descriptions of the same event may be written from various vantage points and submitted. Elements of the protocol that must be logged include the notification algorithm, specifically recording who was called and when. The patient assessment, clinical workup, and treatment plan, including a discussion of current and anticipated side effects, all need to be detailed. Also, personnel should detail information on the monitoring level, reassessment plan, and time frame. Discharge instructions are provided to the patient and documented in the electronic medical record. These include patient expectations and requirements necessary to comply with the increased scrutiny of the treatment and monitoring plan.

Patient and Family Education

The patient will likely have challenging questions that are best addressed by an experienced practitioner. For this reason, the attending oncologist needs to lead patient and family education discussions. A key aspect of this process will be emotional support for the patient and family. Provide an opportunity to discuss the event and express related feelings. Strongly consider involving a social worker to facilitate a supportive discussion. The presence of a patient representative or advocate may be helpful.

Specific information provided to the patient should include the anticipated side effects, what is known about the incident, and what the patient can expect. This may be particularly difficult if little is known about the overdose of a particular agent.

- Keep patient upright if possible.
- Immediately obtain neurology and neurosurgery consultations.
- Transfer patient to a neurologic intensive care unit, as appropriate.
- Drain at least 20 ml of cerebral spinal fluid (as much as 70 ml), if indicated. For best outcome, this should be performed within 15 minutes of the overdose.
- If appropriate, consult neurosurgery service for placement of a vertebral catheter and start ventriculo-lumbar perfusion. Infuse warmed, preservative-free normal saline through ventricular catheter and drain fluid from lumbar catheter. Typical volumes are 80–150 ml per hour for 18–24 hours.
- Administer dexamethasone 4 mg via IV every six hours to prevent arachnoiditis.

FIGURE 3. Procedure for Intrathecal Overdose

Note. Based on information from O'Marcaigh et al., 1996.

Medical personnel should clearly detail the specifics and rationale of the treatment and monitoring plan, and what will be required of the patient and family. In addition to speaking to the patient, personnel should provide the patient with written physician contact information, including 24-hour emergency (answering service) telephone numbers along with instructions to return to the clinic or emergency room should any problems occur. The patient must be directed to go to the nearest hospital in an emergency and bring with them their discharge instructions and physician contact information. The closest hospital may not necessarily be the institution where chemotherapy was administered.

Staff Education

Once this policy and procedure was approved by hospital management, the authors' institution initiated education for oncology physicians, nurses, and pharmacists, with departmental and on-unit reviews. An online education program was developed with a post-test. Testing assessed ability to recognize potential overdose situations and to take appropriate actions. The education was reinforced for nurses by including the protocol in the hospital's annual chemotherapy recertification course. The information also was communicated via poster presentation at the institution's annual safety and quality conference.

Variance Analysis

An essential part of handling a serious chemotherapy variance is an objective analysis of the process failures that led to the error. The institution should initiate a multidisciplinary review of procedures governing chemotherapy order writing, production, and administration. Identification of points of failure and implementation of corrective actions are the primary outcome of the variance analysis. The institution needs to provide staff debriefing and emotional support to staff involved in the incident. Staff directly involved in a chemotherapy variance will likely feel a wide range of emotions, any of which may have unintended ramifications on the process of analysis of the error (Osborne, Blais, & Hayes, 1999). Responsible staff may experience a level of denial or lack of knowledge concerning the potential seriousness of consequences associated with the variance. In addition, individuals may feel shame or embarrassment at not catching a serious error and fear of reprisal from the employer or litigation. Emotional assessment and professional support issues need to be addressed in a timely manner.

Implications for Practice

Chemotherapy overdose is a multidisciplinary event with shared accountability across oncology medicine, nursing, and pharmacy. Multidisciplinary teamwork enables the most efficient response to hopefully minimize morbidity and mortality. Although precisely quantifying the effect of this policy is difficult, a heightened awareness and vigilance has been achieved through staff education regarding early recognition and response for a potential chemotherapy overdose.

Nurses play a vital role in chemotherapy order verification, administration, and patient and family education. By defining criteria for early recognition of a potential overdose, nurses are empowered with the knowledge to rapidly respond, using an established policy for assessment and monitoring. Possible interventions are identified and nurses are provided with a guideline for appropriate patient and family education.

Conclusion

Recognizing and addressing areas of vulnerability in the complex process of chemotherapy delivery is critical to maximizing

TABLE 1. Assessment of Expected Toxicity by System

Expected Toxicity	System Specific Assessment and Medical Plan Option
Bladder	Administer IV hydration if not contraindicated by comorbidities. Consider urology consultation. Consider continuous bladder irrigation.
Cardiac	Obtain electrocardiogram and an echocardiogram to assess ejection fraction. Compare to baseline. Consider administration of dexrazoxane in the setting of immediate anthracycline overdose. Consider cardiology consultation.
Dermatologic	Obtain a dermatology consultation. Assess for exfoliating dermatitis. Consider administration of high-dose corticosteroids.
Gastrointestinal	Provide supportive care with antiemetic drugs. Administer antidiarrheal drugs for diarrhea. Administer analgesics, antibiotics, and topical treatments for mucositis per institution standards.
Hepatotoxicity	Obtain liver function tests and coagulation parameters. Avoid drugs that interact with hepatic metabolic pathways, such as cytochrome P450 pathways.
Myelosuppression	Begin filgrastim more than 24 hours after chemotherapy completion. Consider prophylactic antibiotics. Assess for signs and symptoms of bleeding. Test stool and emesis for blood.
Neurologic	Perform neurologic assessment. Obtain neurology and neurosurgery consultation if overdose involves intrathecal drugs.
Pulmonary	Obtain chest x-ray. Obtain pulmonary function tests and compare to baseline, if available. Consider use of corticosteroids. Consider pulmonology consultation.
Renal	Administer IV hydration if not contraindicated by comorbidities. Avoid additional nephrotoxic drugs. Obtain audiogram if cisplatin overdose. Closely monitor renal function and urine output; if methotrexate, maintain urine pH 7–8 range. Consider a nephrology consultation.

TABLE 2. Potential Interventions in the Event of Chemotherapy Overdose

Intervention Agent	Dose and Administration	Monitor
Methotrexate (IV, IM, PO, systemic administration)		
Glucarpidase (Solimando, 2012; Widemann et al., 2010)	50 units/kg (each vial contains 1,000 units of glucarpidase to be reconstituted with 1 ml of sterile saline); single bolus IV push for five minutes	Methotrexate serum levels, serum creatinine, urine output, urine pH, and bone marrow function
IV fluids with sodium bicarbonate (Rahiem Ahmed & Hasan, 2013; Solimando, 2012)	Add 50 mEq to each liter of IV hydration.	Urine pH (range 7–8)
Leucovorin (Solimando, 2012)	Pharmacokinetic guided leucovorin rescue until methotrexate level is less than 0.05 micromole per liter (5×10^{-8} M)	Methotrexate serum levels, serum creatinine, urine output, urine pH
Methotrexate (IT administration)		
Dexamethasone (Solimando, 2012)	4 mg IV push every six hours for duration of four doses	–
Glucarpidase (not FDA approved for IT use) (Bradley et al., 2012; O'Marcaigh et al., 1996)	2,000 units in 12 ml preservative-free normal saline administered via IT injection	–
Leucovorin (Solimando, 2012)	Pharmacokinetic-guided leucovorin rescue until methotrexate level is less than 0.05 micromole per liter (5×10^{-8} M)	Methotrexate serum levels, renal function, urine output, and urine pH
Vincristine		
Bowel regimen (Solimando, 2012)	Schedule stimulant laxative and stool softener.	Bowel function
Cholestyramine (Solimando, 2012)	Adult: 4 g twice daily Pediatric: 240 mg/kg per day in three divided doses	Treat for constipation.
Leucovorin (Grush & Morgan, 1979; Thomas et al., 1982; Vik et al., 1985)	10–15 mg/m^2 every three hours for the duration of 24 doses	LFT, cardiac function, neurologic function or seizures, bone marrow function, and SIADH
Sincalide (Jackson et al., 1982)	0.01 mcg/kg per hour continuous infusion in 250–1,000 ml D5W. Continue until ileus is resolved.	Bowel function; discontinue sincalide if patient develops diarrhea.
5-Fluorouracil (5-FU)		
Uridine triacetate (Doroshow et al., 2006; Hidalgo et al., 2000; Saif et al., 2007)	Orphan-drug designation (not approval) by FDA; available from WellStat Therapeutics, Inc. and the FDA with an emergency IND	Cardiac status
Cisplatin		
Sodium chloride diuresis (Leu & Baribeault, 2010; Morgan et al., 2012)	0.9% sodium chloride hydration with or without mannitol	Urine output (maintain at 1–3 ml/kg per hour for 6–24 hours after exposure)
Sodium thiosulfate (Erdlenbruch et al., 2002)	Loading dose: 4 g/m^2, followed by maintenance 2.7 g/m^2 per day (divided three times per day); continue for duration of 7–14 days. Therapy must be administered within 1–2 hours after exposure.	Blood pressure, CNS status, renal function, serum electrolytes, ECG, nausea, and vomiting. Provide adequate antiemetic drugs for both acute and delayed emesis.
Arsenic trioxide		
Dimercaprol (adults) (Solimando, 2012)	3 mg/kg IM every four hours until life-threatening toxicity subsides, then begin penicillamine.	Cardiac status, ECG (Q-T interval), coagulation status, serum electrolytes, LFT, neurologic status, and respiratory status. Provide adequate antiemetics. Consider 24-hour urine for arsenic levels (specimen to be sent out to reference laboratory).

(Continued on the next page)

CNS—central nervous system; D5W—dextrose 5% in water; ECG—electrocardiogram; FDA—U.S. Food and Drug Administration; IM—intramuscularly; IND—investigational new drug; IT—intrathecal; LFT—liver function test; SIADH—syndrome of inappropriate antidiuretic hormone

TABLE 2. Potential Interventions in the Event of Chemotherapy Overdose *(Continued)*

Intervention Agent	Dose and Administration	Monitor
Arsenic trioxide *(Continued)*		
Penicillamine (adults) (Solimando, 2012)	Give after a course of dimercaprol is completed. Begin chelation therapy with penicillamine 250 mg PO 3–4 times per day (total daily dose of 1 gm per day or less).	Diarrhea and neurologic status
Ifosfamide		
IV fluids (Solimando, 2012)	IV hydration; maintain urine output 1–3 mg/kg per hour for a duration of 24 hours after exposure	Monitor output and urinalysis for blood.
Mesna (Solimando, 2012)	Dose is 100% of ifosfamide dose, given as 20% every two hours for a duration of five doses	Monitor output and urinalysis for blood.
Methylene blue (Patel, 2006)	50 mg IV as a 1% solution	Neurologic status, urine output, renal function, bone marrow function, hepatic enzymes, and hematuria
Thiamine (Hamadani & Awan, 2006)	100 mg IV every three hours	Neurologic status
Oral chemotherapy agents		
Activated charcoal (Solimando, 2012)	Mixed as slurry (30 g charcoal in 240 ml water). Dose is based on age: adults, adolescents, 25–100 g; children (1–12 years), 25–50 g; infants (younger than 1 year), 1 g/kg	–
Gastric lavage (Solimando, 2012)	Gastric lavage with airway protection if performed within one hour of ingestion	–

CNS—central nervous system; D5W—dextrose 5% in water; ECG—electrocardiogram; FDA—U.S. Food and Drug Administration; IM—intramuscularly; IND—investigational new drug; IT—intrathecal; LFT—liver function test; SIADH—syndrome of inappropriate antidiuretic hormone

safety. Despite a robust set of safety precautions already in place, errors still can occur. Much has been published on essential safety systems that focus on error prevention; however, implementing a rational plan in the event of a potential overdose situation also is needed to optimize the safety net provided to patients receiving chemotherapy drugs. A clearly defined, rapid response for chemotherapy variance delineates assessment responsibility and provides general information on monitoring and potential treatment options that must be initiated without delay to decrease patient morbidity and mortality. This plan educates and guides staff about immediate actions to take if the systems do not prevent error.

Implications for Practice

- Establish practice guidelines that facilitate early recognition and immediate actions following a potential chemotherapy overdose.
- Identify potential therapeutic interventions and system-specific assessments to promote patient safety.
- Educate patients and family members regarding the treatment plan and required monitoring to achieve the optimal outcome after a chemotherapy overdose.

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