

Cytotoxic drug: Towards safer chemotherapy practices

Joshi MC

Clinical Pharmacologist, Prescription Audit Department, Indraprastha Apollo Hospital, Delhi Mathura Road, Sarita Vihar, New Delhi - 110 076, India

Correspondence to: Mukesh Chandra Joshi, E-mail: drjoshimukesh@rediffmail.com

Abstract

Health care is nearly 10 years behind other industries in its efforts to reduce the errors. Medication error may be nobody's baby, but when it happens, it could well turn out to be everyone's worry and the reasons given for medication error range from silly to the downright serious. The anticancer drugs are known to be mutagenic, teratogenic and carcinogenic, so extra precaution should be taken while storing, diluting, administering the drugs and disposing the waste. The objectives of this article are to define the standards for using cancer chemotherapy in hospitals; to tackle any spillage of drug and how to dispose of the waste of anticancer drugs. This could be beneficial to any hospital where chemotherapy is given without any defined standard operating procedure. The information furnished in this article is collected from the mentioned references and also from websites- The American Cancer Society: Cancer Facts and Figures 2002, www.cancer.org and www.cancersourceRN.com

Key words: Carcinogenic, mutagenic, teratogenic

Introduction

The problem of medication safety came to public attention largely through a chemotherapy error and the high toxicity and low therapeutic index of anticancer medications make safety in their prescription and administration critical. The anti cancer drugs are known to be mutagenic, teratogenic and carcinogenic therefore all efforts must be done to reduce accidents from cancer chemotherapy and to implement safe chemotherapy practices.

Safe Chemotherapy Practices Program

The problem of medical errors came to focus a decade back because of certain noticeable accidents such as the death of *Boston Globe* medical writer Betsy Lehman, 12 years ago due to an overdose of chemotherapy.^[1] Oncologists have no greater or lesser chance of erring than most other physicians, but the high toxicity and small therapeutic index of the drugs they prescribe make chemotherapy errors potentially catastrophic. After the Lehman incident, many hospitals and practices examined their chemotherapy ordering practices and put new

safeguards in place and a vast majority of comprehensive cancer centers, university hospitals and community hospitals had begun chemotherapy safety programs.^[2]

Prescription of Cytotoxic Drugs

The cytotoxic drug order by the oncologist is sent to the pharmacy at least one hour in advance of the anticipated administration time. These orders contain all the relevant hand written information regarding the drug (brand and generic name, cost, rate and route of administration, diluents to be used, filter to be used) and are labeled as chemotherapy order sheet. These prescription orders in some hospitals are sent to the pharmacist using computer software to reduce the chances of transcription errors, but still in many hospitals in India they are hand written. The cytotoxic drug prescription should contain all the relevant information regarding the drug, the doses according to body wt or body surface area (BSA), the diluents to be used, infusion rate, route of administration, the diagnosis of the patient. All doses should be calculated independently by the physician, the pharmacist and the

nurse. Dosage limits should be established and a review process set up for doses that exceed the limits. These limits should be entered into the pharmacy computer systems, listed on preprinted order forms, stated on the product packaging, placed in strategic locations in the institution and communicated to employees.^[3]

Now days computerized software programmes are available to reduce the errors of transcription. This software calculates the appropriate doses once weight/BSA or other relevant information of the patient is fed and also raise alarms in case wrong infusion fluid or rate or IV line filter is used.

Validation of Prescription by a Pharmacist

An onco-pharmacist is responsible for checking the rationality of chemo-medication ordered by the consultants. The onco-pharmacist checks the chemotherapy order for right diluents, right doses and right route of administration. He reviews the profiles of the patients and verifies that all labels are written correctly. A second pharmacist shall verify that the order has been profiled and entered into the computer correctly and shall initial the profile to the left of the drug name. Medication errors are common to occur if cross checks are not done regularly and while most such errors have little potential for harm they cause substantial extra work in hospitals. A small proportion do have the potential to cause injury and some cause preventable adverse drug events. Some studies suggest computerized physician order entry (POE) with decision support to decrease the rate of non-missed-dose medication errors.^[4]

Although information technologies are widely used in hospitals, relatively few data are available regarding their impact on the safety of the process of giving drugs. Exceptions are computerized physician order entry and computerized physician decision support, which have been found to improve drug safety.^[5-7]

Computerized POE

Computerized POE is an application in which physicians write orders online. This system has probably had the largest impact of any automated intervention in reducing medication errors; the rate of serious errors fell 55% in one study^[6] and the rate of all errors fell 83% in another.^[4] Computerization of ordering improves safety in several ways: firstly, all orders are structured, so that they must include a dose, route and frequency; secondly, they are legible and the orderer can be identified in all instances; thirdly, information can be provided to the orderer during the process; and fourthly,

all orders can be checked for a number of problems including allergies, drug interactions, overly high doses, drug-laboratory problems (giving a patient a drug when they have a known biochemical factor that predisposes them to risk) and whether the dose is appropriate for the patient's liver and kidney function. Other innovations, which include using robots to fill prescriptions, bar coding, automated dispensing devices and computerization of the medication administration record, though less studied, should all eventually reduce error rates.

These orders have to be prepared as soon as possible. If a drug is needed immediately and no pharmacist is available to make the admixture, then a duty doctor / nurse of oncology department may use the pharmacy hood to prepare the admixture. The anticipated administration time shall clearly be indicated on the pharmacy copy of the physician order. A Checklist before preparing the cytotoxic drugs is made which is called the chemotherapy order sheet.^[3]

This chemotherapy order sheet includes the following things:

1. Name of the drug, company name, active salt, strength and expiry date
2. Patient name, age and patient ID number
3. Number of chemotherapy cycle
4. Approximate cost of the drug
5. Drug delivery route and access devices
6. Solvent and its concentration in which it is to be mix
7. Infusion or diluents fluids (D5%W / NS / RL / DNS) with which to be mixed
8. Availability of drug delivery access
9. Cross marking of the pack and label of the vial / ampoule
10. Premedication as prescribed is given
11. Drug dose according to body surface area / body weight

Procedures of Safe Cytotoxic Drug Reconstitution

Cytotoxic drug dilution is an important part of cancer chemotherapy. It should be carried out separately in a cytotoxic admixture unit and not in the wards because of the danger from spillage and contamination. Class II cabinets are the recommended safety cabinets for drug dilution under laminar flow.^[2] Class II cabinets are part-recirculation laminar airflow enclosures with HEPA filtration of exhaust air and an air barrier at the work opening. Separate fan/HEPA filter systems are provided for exhaust and laminar air flow. Cytotoxic drug safety cabinets are similar to class II cabinets in terms of

operator and product protection. They also overcome the problem of protecting maintenance personnel by locating the exhaust filter under the work surface. They provide environmental and product protection.^[8]

Precautions during dilution of cytotoxic drugs

All precautions must be taken to reduce direct contact whether through skin exposure, inhalation or ingestion. Adequate facilities for drug preparation are essential to reduce the risk of exposure. The following points are important.^[9-12]

1. Wear latex powder free long cuff gloves while preparing chemotherapy drugs. Wear a gown that is low or non-permeable, long sleeve, cuffed and solid fronted and use aerosols free mask.
2. Work over a suitable container to prevent the spread of any spillage.
3. Prevent high pressure being generated inside sealed vials - when fluids are introduced an equivalent volume of air should be withdrawn or a venting needle with a hydrophobic filter (to prevent aerosol formation) may be used if available.
4. Ampoules should be directed away from the face and covered with a suitable pad or cotton when broken open.
5. Diluent fluids should be introduced slowly into open-ended ampoules or vials, running it down the vessel wall and ensuring the drug powder is moist before shaking.
6. When excess air is expelled from a filled syringe it should be exhausted into a pad and not straight into the atmosphere.
7. If excess drug is to be expelled from a filled syringe it should be removed first and sterile cotton wool placed over the end of the syringe to prevent possible scatter of aerosol droplets.
8. Luer lock fittings should be used on syringes, tubing and I.V. sets.
9. Label all prepared bottles (It is mandatory).
10. Admix all cytotoxic drugs in class II biological safety cabinet (laminar air flow) that meets standards and it is inspected appropriately.
11. Check the reconstitute or diluents for the particular drug and the concentration in which it is reconstituted.
12. The cytotoxic drug after reconstitution should be administered as soon as possible. Before reconstitution it should be stored at cold refrigerator temperature of 2-8°C (36°F - 46°F) or controlled room temperature of 15-30°C (59-86°F) depending on the product. Protect from light. After reconstitution with the provided or appropriately selected diluents always store at cold

refrigerator temperature of 2-8°C (36°F - 46°F). Do not refrigerate the reconstituted product. The duration of stability after reconstitution varies with chemical composition of the compound but usually if stored at cold refrigerator temperature of 2-8°C (36°F - 46°F) the reconstituted product is stable for at least 24h.

Administration of cytotoxic drugs in the ward or outpatients

The practice of preparing cytotoxic drug in the wards or outpatients should be discouraged because of the danger of spillage and higher chances of exposure of the personnel involved in preparing. If a drug is needed immediately and no pharmacist is available to make the admixture, then a duty doctor / nurse of oncology department may use the pharmacy hood to prepare the admixture. If however a cytotoxic admixture unit is not established in a hospital then in the wards or outpatients a proper place should be fixed and all the precautionary measures to avoid exposure like wearing latex powder free long cuff gloves, a gown that is low or non-permeable, long sleeve, cuffed and solid fronted, aerosols free mask. A spillage kit should be kept near by to tackle the cytotoxic drug spillage.

Management of spillage of cytotoxic drugs^[11-15]

The spillage of cytotoxic drugs should be handled with utmost care. A proper procedure must be implemented for spillage and it should be treated appropriately. On spillage of cytotoxic drugs on body parts an appropriate treatment should be given according to Tables 1 and 2. The admixture room should have a spill kit with the following items:

1. Phosphate buffer pH 7.4 9. Powder free gloves - 2 pairs
2. DMSO (dimethylsulfoxide) 100% 10. Aerosols free mask and head cap - 1
3. Hypochlorite ointment FNA 0.25% 11. Absorbent towel - 2, 12"x12"
4. Sodium thiosulphate 10% 12. Scoop and brush - 1 set
5. Sodium carbonate solution 3% 13. Eye glass - 1
6. Sodium hypochlorite 5% 14. Cytotoxic disposal poly bag - 1
7. 0.1N hydrochloric acid 15. Gown poly coated - 1
8. Alcohol 70% 16. Shoe covers - 1 pair

Disposal of waste materials

The waste material generated after cytotoxic drug admixing like syringe, needle, mask and gloves should be disposed carefully in cytotoxic disposal bags. A standard procedure is to be made and followed for disposals of waste materials. The disposal bags should

Table 1: Treatment of cytotoxic drugs spillage**A. Skin contact****Treatment given**

- If the skin is damaged, the wound should be treated as extravasations.
- Warn others and make it clear if you need help
- Immediately remove gloves or clothes. The hands and skin under the clothes are to be regarded as contaminated
- Follow these specific measures:
 1. Rinse with sodium carbonate solution 3%
 2. Rinse with large amounts of water
 3. Disinfect with alcohol 70%
 4. Rinse with phosphate buffer pH 7.4

B. Eye contact**Treatment given**

- Ask others for help if possible
- Follow these specific measures:
 5. Immediately rinse the eyes with large amounts of water for 10 minutes
 6. Rinse the eyes with phosphate buffer pH 7.4

C. Extravasation**Treatment given**

- Stop the administration; keep the infusion needle in position and elevate the arm
- Draw blood, 3-5 ml if possible, in order to remove as much cytostaticum as possible
- Follow these specific measures:
 7. Cool with cold packs for 15 minutes
 8. Consult a (plastic) surgeon
 9. Apply intermittent cold packs for 24h. Every 3h of cooling should be interrupted for 30 minutes
 10. Infiltrate with 5 ml of sodium thiosulphate 4%
 11. Apply DMSO 100% topically and allow to air-dry four times daily for 14 days
 12. Treat with hypochlorite ointment FNA 0.25% (formerly Eusol)
 13. Infiltrate with hyaluronidase (1 ml = 150 I.E.)
 14. Apply hot packs to the extravasations site.
 15. Infiltrate with 4 ml of sodium thiosulphate 10%.

D. Inactivation- To render the cytotoxic drug inactive**Treatment given**

16. Rinse with sodium carbonate solution 3%
17. Rinse with phosphate buffer pH 7.4
18. Sodium hypochlorite 0.5% in water = household bleach
19. Disinfect with alcohol 70%
20. 0, 1N hydrochloric acid

Table 2: Specified treatment for individual cytotoxic drugs spillage

Drug	Skin contact	Eye contact	Extravasation	Inactivation
Aldesleukin	2	5	7	-
Amsacrine	2	5	7+8	-
Asparaginase	2	5	*	-
Azathioprine	2	5	-	18
BCG-vaccine	2+3	5	-	19
Bleomycin	2	5	7	18
Carboplatin	2	5	7	-
Carmustine	2	5	8	-
Chlormethine	1+2	5	8+9+10	16
Cisplatin	2	5	7	-
Cladribine	2	5	-	-
Cyclophosphamide	2	5	7	-
Cytarabine	2	5	*	-
Dacarbazine	2	5	7	-
Dactinomycin	4	6	8+9+11	17
Daunorubicin	2	5	8+9+11	18
Docetaxel	2	5	-	-
Doxorubicin	2	5	8+9+11	18
Epirubicin	2	5	8+9+11	18
Estramustine	1+2	5	8+9+10	16
Fluoposide	2	5	*	18
Flucarbazine	2	5	-	-
Fluorouracil	2	5	*	18
Ganciclovir	2	5	-	-
Gemcitabine	2	5	-	-
Idarubicin	2	5	8+9+11	18
Ifosfamide	2	5	7	-
Interferon alfa	2	5	-	-
Irinotecan	2	5	-	-
Melphalan	2	5	7	-
Methotrexate	2	5	*	-
Mitomycin	2	5	8+9+11+15	20
Mitoxantrone	2	5	7+12	18
Oxaliplatin	2	5	7	-
Paclitaxel	2	5	14	-
Pentostatin	2	5	-	18
Raltitrexed	2	5	-	-
Streptozocin	2	5	-	-
Teniposide	2	5	-	-
Thiotepa	2	5	7	-
Topotecan	2	5	*	-
Vinblastine	2	5	8+13+14	18
Vincristine	2	5	8+13+14	18
Vinorelbine	2	5	8+13+14	18

*No health risks - No data available

Note: The numbers written in the columns are the actions to be taken on exposure of the respective cytotoxic drug. These numbers are explained in Table 1.

print with cytotoxic drug.

Cytotoxic waste is highly hazardous and should never be land filled or discharged into the sewerage system. Disposal options include the following.^[16]

1. Return to original supplier: This is currently the preferred option for countries that lack the facilities for incineration.
2. Incineration at high temperatures: Modern double-chamber pyrolytic incinerators are suitable, provided that a temperature of 1200°C with a minimum gas residence time of 2 seconds or 1000°C with a minimum gas residence time of 5 seconds can be achieved in the second chamber. The incinerator should be fitted with gas cleaning equipment.
3. Chemical degradation: Most of these methods are relatively simple and safe; they include oxidation by potassium permanganate (KMnO₄) or sulphuric acid (H₂SO₄), denitroization by hydro bromic acid (HBr) or reduction by nickel and aluminium. The International Agency for Research on Cancer (IARC) (Unit of Gene-Environment Interactions, 150 Cours Albert-Thomas, 69372 Lyon Cedex 08, France) may be contacted for further information.

Maintenance of records and incident forms

The hospital should maintain the records of patients receiving cytotoxic drugs. Every detail regarding the cytotoxic drug used and how it was prepared etc. Incident form should be filled in case of any error in the process. Any spillage of the cytotoxic drugs is notified.

Audit of the cytotoxic drugs usage

The whole process of cytotoxic drug admixture and administration should be handled very carefully because any error occurring in the process is bound to be a serious one. Periodic review of cytotoxic drugs administration practices, as well as an analysis of any error committed, is necessary to develop optimal patient care. There are reports of using rapid cycle change method, which could be helpful in driving out fear and a fair reporting of errors and learning from them.^[1] Every institution should have a quality assurance and audit plan in place which details the process for responding when an error has been made and methods for counseling the health care providers involved. Committees formed to address these issues should include representatives of all disciplines involved in medication ordering, preparation and administration.

Conclusion

This review study focuses on the important aspect of

safe chemotherapy practices, which not only includes safe handling, proper dilution and dispensing in cytotoxic admixture unit, but also the management of any spillage of cytotoxic drugs in the hospital and disposal of the biohazardous waste generated by the use of cytotoxic drugs. Since, these drugs have a high toxicity an utmost care and precautions is to be taken while handling preparing, administering and disposing.

References

1. Womer RB, Tracy E, Soo-Hoo W, Bickert B, DiTaranto S, Barnsteiner JH. Multidisciplinary systems approach to chemotherapy safety: Rebuilding processes and holding the gains. *J Clin Oncol* 2002;20:4705-12.
2. Dinning C, Branowicki P, O'Neill JB, Marino BL, Billett A. Chemotherapy error reduction: A multidisciplinary approach to create templated order sets. *J Pediatr Oncol Nurs* 2005;22:20-30.
3. Cohen MR, Anderson RW, Attilio RM, Green L, Muller RJ, Pruemer JM. Preventing medication errors in cancer chemotherapy. *Am J Health Syst Pharm* 1996;53:737-46.
4. Bates DW, Teich JM, Lee J, Seger D, Kuperman GJ, Ma'Luf N, *et al.* The impact of computerized physician order entry on medication error prevention. *J Am Med Inform Assoc* 1999;6:313-21.
5. Bates DW. Using information technology to reduce rates of medication errors in hospital. *BMJ* 2000;320:788-91.
6. Bates DW, Leape LL, Cullen DJ, Laird N, Petersen LA, Teich JM, *et al.* Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *JAMA* 1998;280:1311-6.
7. Vanderbroncke J, De Cock P, Robays H. Influence of a computerized program on the quality of prescribing and preparing cytotoxic drugs. *J Oncol Pharm Practice* 2004;10:61.
8. Wick C, Slawson MH, Jorgenson JA, Tyler LS. Using a closed-system protective device to reduce personnel exposure to antineoplastic agents. *Am J Health Syst Pharm* 2003;60:2314-20.
9. Oncology nursing society: ONS cancer chemotherapy guidelines and recommendations for practice. Oncology Nursing Society Press; Pittsburgh; 1999.
10. Rutherford C. Position paper-Administration of antineoplastic agents. *J Intraven Nurs* 1992;15:8-9.
11. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm* 1990;47:1033-49.
12. American society of hospital pharmacists: Safe handling of cytotoxic and hazardous drugs study guide. American Society of Hospital Pharmacists: Bethesda MD; 1990.
13. Vandenbroucke J, Robays H. How to protect environment and employees against cytotoxic agents the ghent experience. *J Oncol Pharm Practice* 2001;6:146-52.
14. Kiffmeyer TK, Kube C, Opiolka S. Vapour pressure, evaporation behavior and air borne concentration of hazardous drugs: Implication for occupational safety. *Pharm J* 2000;268:331-7.
15. Sessink PJ, Wittenhorst BC, Anzion RB, Rob RP. Exposure of pharmacy technicians to antineoplastic agents: Reevaluation after additional protective measures. *Arch Environ Health* 1997;52:240-4.
16. Safe management of wastes from health care activities. WHO: 1999. Available from: http://www.who.int/cytotoxic_waste_management.

Source of Support: Nil, Conflict of Interest: None declared.