

## ***Guidelines on the handling of cytostatic drugs outside hospitals***

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### ***Preface***

Treatment of cancers with cytostatic drugs can be carried out outside hospital so that patients can receive care and treatment in their own home or at a medical centre, at their doctor's or at a nursing home close to where they live. It is important that patients and their relatives can be confident that the treatment is carried out in just as safe a manner as in hospital. One condition for this is that nurses/doctors have mastered the handling of cytostatic drugs.

According to the Supply of Medicines in Local Authority Health Services Order of 18 November 1987 (1), no preparation of medicines may take place within local authority health services. Exempted from these provision are preparations which, because of a short shelf life, have to be prepared immediately before use or for rapid consumption (dry ampoules and similar), and the addition of sterile medicines to infusion bags immediately before use (§ 7). The preparation of cytostatic drugs for use in local authority health services should therefore be carried out, as far as is practically possible, by a pharmacy in order to ensure the necessary quality of preparation. However, pre-prepared solutions of cytostatic drugs often have a very short shelf life and it may then become necessary for the preparation to be carried out in situ prior to administration. In addition, the Norwegian Labour Inspection Authority laid down regulations for the handling of cytostatic drugs on 18 December 1980. The Norwegian Board of Health has learned from experience that outside hospital cytostatic drugs are often handled without the necessary aids and without special training being given. In primary care, guidelines have been put into effect for handling cytostatic drugs in nursing homes.

Handling of cytostatic drugs includes both the preparation of ready-to-use drugs and administration of those drugs to the patient, and the guidelines therefore cover both aspects.

The Norwegian Board of Health asked the Norwegian Association of Hospital Pharmacists [Norske Sykehusfarmasøytters Forening] for assistance in this work. The chemotherapy specialist group of the Norwegian Association of Hospital Pharmacists developed a proposed set of guidelines. The members of the specialist group were hospital pharmacists:

Gunn Fredriksen, Trondheim Regional Hospital, Trondheim; Kirsten Myhr, Trondheim Regional Hospital; Kari Smørdal, Hospital Pharmacist in Molde.

The proposal was submitted to hearing after which further work was done on it by Helge Nordahl, a pharmacist at the Radiumhospitalet's pharmacy, in collaboration with the Norwegian Board of Health. The Norwegian Board of Health would like to thank the Norwegian Association of Hospital Pharmacists and the pharmacy of Radiumhospitalet for a job well done.

The Norwegian Board of Health hopes that these guidelines will contribute to the safe handling of cytostatic drugs outside hospital.

Anne Alvik

Health Director

## **What are cytostatic drugs?**

Cytostatic drugs are medicines that are used in the treatment of cancer. In some circumstances they are also used for rheumatic conditions and skin diseases. They are part of ATC group L01 (yellow pages of the Pocket Catalogue).

Cytostatic drugs damage or kill cancerous cells by affecting their genetic material. Since the drugs act on all growing cells, they also affect normal cells and can cause serious side effects.

### ***Important!***

Everyone who is responsible for or actually supervises the task of preparing or administering cytostatic drugs to patients, must have received the necessary training (2) and should

- have studied these guidelines
- follow the Norwegian Labour Inspection Authority's rules on handling cytostatic drugs (2)
- have available the handbook "Cytostatic drugs. Medical Treatment of Cancer", hereinafter referred to as the manual (3)
- have and use personal protective equipment (see Personal protective equipment)
- have considered and taken precautions against any problems which might arise during the preparation.

## **Regulations and risks**

### *Rules for handling cytostatic drugs*

The Norwegian Labour Inspection Authority has laid down its own regulations on the handling of cytostatic drugs (2). The regulations include

- requirements on equipment and premises for making up patient doses
- requirements for personal protective equipment
- requirements for waste handling
- requirements for training of staff who handle cytostatic drugs
- ban on pregnant women and employees with a relevant medical certificate working with cytostatic drugs
- requirements for registration of staff who regularly work with cytostatic drugs.

### *Risk to staff*

The risk to staff who handle cytostatic drugs is greatest when making up and administering preparations for injection/infusion. Contamination of the skin and inhalation of aerosol (see page 10) can have systemic effects and must be avoided. Furthermore, many cytostatic drugs are highly irritating to the skin and can damage unprotected skin.

Cytostatic drugs can be carcinogenic and cause foetal damage at therapeutic doses. It is

known that occupational handling of cytostatic drugs without adequate protective measures can cause genetic damage. On the other hand the risk to health is minimal if staff protect themselves and their environment from contact with the material (see Regulations on Handling of Cytostatic Drugs).

#### *Ban on working with cytostatic drugs*

Pregnant women and employees with medical certificates stating that they should temporarily or permanently not work with cytostatic drugs must be transferred to work in which they do not handle and are not exposed to cytostatic drugs (Regulations on Handling of Cytostatic Drugs, § 5).

#### *Training and information*

All staff who are to work with cytostatic drugs must have appropriate training and the requisite information about different aspects of handling them. With adequate knowledge and skills cytostatic drugs can be handled properly and safely. The Regulations on Handling of Cytostatic Drugs, § 3, lay down requirements for the employer on giving the necessary training. Local authority supervisory pharmacists and pharmacists at the local pharmacy can give or obtain advice on handling cytostatic drugs. Practical experience at a hospital pharmacy and contact with cancer nurses at a hospital may also form part of the training.

Anyone who is to be responsible for administering cytostatic drugs must have experience of venepuncture so as to reduce the danger of tissue damage during infusion/injection. Knowledge of the effects/side effects is also required in order to be able to answer questions from patients and relatives and to manage situations that may arise in relation to the effects/side effects of the drugs.

### **Arrangement of cytostatic drugs in conjunction with the hospital**

#### *Collaboration with the hospital*

When patients are to receive continued chemotherapy under the auspices of the primary care service after discharge from hospital, it is both desirable and necessary for the primary care service to contact the discharging unit with regard to treatment. In most cases questions about the preparation and administration of cytostatic drugs can also be answered by the hospital pharmacy concerned, the pharmacy department or the supervisory pharmacist.

#### *Arranging cytostatic drugs for patients*

There must be a written prescription for the individual patient from a doctor, stating the drug, dose, method of administration and any diluent (e.g. sodium chloride 9 mg/ml or glucose 50 mg/ml) and the quantity thereof. See whether there are any instructions in the epicrisis (summary of the patient's case, course of the illness, and therapy) from the hospital. In case of doubt, see the chapters on the handling and administration of cytostatic drugs in the handbook (3), Pocket Catalogue or pack information sheet, or else contact the hospital.

With drugs where a check on blood values is required before the next dose, a blood sample must be taken and the result made available before the preparation and administration of cytostatic drugs is carried out.

#### *Can the preparation be obtained from the pharmacy ready to use?*

As stated in the preface, the preparation of ready-to-use solutions of cytostatic drugs should be carried out by a pharmacy. All independent pharmacies can supply courses of cytostatic drugs.

When parenteral chemotherapy is to be performed in primary care, the unit discharging the patient should contact the local pharmacy or the hospital pharmacy closest to the patient's home in plenty of time, possibly via the hospital pharmacy or the hospital's pharmacy department. Individual pharmacies may take some time to prepare deliveries of ready-to-use preparations for the first time. The regulations on handling cytostatic drugs (2) must be complied with.

Supply from the pharmacy is to be preferred where it is practically possible. Pre-prepared courses of cytostatic drugs have a short shelf life, commonly 24 hours or less. The time and method of delivery must therefore be agreed exactly.

If supplying ready-to-use preparations by these means proves impossible, the preparation can be made up on site by a doctor or nurse immediately before it is administered. The doctor responsible for organising the medical service is also medically responsible for the supply of medicines, including their preparation (see 1, § 2). This guidance from the Norwegian Board of Health should be followed. Two people should check and sign for the calculation and preparation.

### **Preparation of cytostatic drugs**

#### *Premises and equipment for preparation*

A special room or fume extraction bench is not required when cytostatic drugs are seldom handled (Regulations on Handling of Cytostatic Drugs, § 1). Preparation should, however, take place in a shielded draught-free place (not in front of an open window!), preferably with a hand basin nearby. The workbench should be covered with a sheet with an absorbent upper side and a water-proof lower side. Sharps containers for needles and ampoules should be ready as should plastic bags and cartons for other hazardous waste.

Equipment used in preparation commonly includes transfer needles, infusion fluids (saline 9 mg/ml, glucose 50 mg/ml and sterile water) in bags of various sizes, syringes of suitable dimensions, 19 G aspiration needles (no larger), sterile compresses and alcohol swabs. When aspirating from glass ampoules, filters – preferably of the flexible fibre type – should be used. Syringes should preferably be of polypropylene and have a *Luer lock* tip.

The infusion set should be a Y-type or four-way set with filter. The set should be filled with infusion fluid from the bag or from a branched saline drip *before* cytostatic drugs are added.

The pharmacy has a summary of and can procure the equipment in question.

#### *Personal protective equipment*

Plastic gloves must not be used when preparing cytostatic drugs. Use thick latex gloves, a shirt or jacket with long sleeves and close-fitting cuffs, and possibly special water-repellent arm protectors. When working without a safety bench, safety glasses and breathing protection (mask approved for protection against solid and liquid particles) should be used in addition. Surgical masks do not provide adequate protection! Gloves should be changed at least every half hour. After use the gloves should be removed by turning them inside out and placed in a waste bag immediately. Arm protectors should be disposed of. Jackets should be placed in the normal laundry receptacle.

Personal protective equipment that has been used in the preparation or administration of

cytostatic drugs, must be removed immediately after use and should not be used in other places.

#### *Preparation of cytostatic drugs*

This section will deal only with preparation of short infusions ("minibags") and syringes. Administration of preparations or doses that require a large volume of fluid will not normally be an issue outside hospital.

Lay out all the necessary equipment before preparation begins.

#### *Transferring solutions of cytostatic drugs to a minibag*

Solutions of cytostatic drugs are most easily transferred to the bag by means of a syringe. The bags are elastic and permit some overfilling. The elasticity varies with the type of bag, so it may be advisable to set an upper limit on overfilling of approx. 10%. If the extra volume becomes too large, some fluid must first be removed from the bag.

The quantity to be transferred to the bag is calculated thus:

$$\frac{\text{Dose (mg)}}{\text{Concentration in vial (mg/ml)}} = \text{Quantity (ml)}$$

Example:

A dose of 750 mg 5-fluorouracil is to be taken from a solution with a concentration of 50 mg/ml. Question: How many ml must be taken to get 750 mg fluorouracil? Calculate the quantity thus:

$$\frac{750 \text{ mg}}{50 \text{ mg/ml}} = 15 \text{ ml}$$

Answer: 15 ml of solution contains 750 mg 5-fluorouracil.

#### *Transfer of solid cytostatic drugs to a minibag*

When the entire contents of a vial is to be transferred to a minibag, this is most easily done by using a transfer needle. Although the transfer needle is easy to use, it can also become contaminated during this process. Inexperienced users are therefore recommended to practice the transfer technique first (bag and vial with saline or similar). Study the instructions that accompany the transfer needle.

Where only part of the solid content of a vial is to be transferred, the following procedure is recommended: withdraw the correct quantity of solvent from the bag with a syringe and dissolve the contents of the vial to the recommended concentration (see pack enclosure). The quantity to be transferred to the bag is calculated thus:

$$\frac{\text{Dose (mg)}}{\text{Concentration in vial (mg/ml)}} = \text{Quantity (ml)}$$

Example:

A dose of 40 mg cytarabin is to be taken from a vial containing 100 mg of solid. Procedure: dissolve all the solid in 5 ml sodium chloride solution from the minibag to a concentration of 20 mg/ml.

Question: How many ml must be withdrawn to get 40 mg cytarabin?

Calculate the quantity thus:

$$\frac{450 \text{ mg}}{\text{mg/ml}} = 2 \text{ ml } 20$$

Answer: 2 ml solution contains 40 mg cytarabin.

#### *Aerosol formation*

When liquid is forced through a narrow opening, e.g. between a rubber stopper and the outside of a needle, it will divide into tiny aerosol droplets which can remain suspended in the air for a long time. Such leaks occur frequently but are by no means always detected. The problem can be reduced with appropriate methods: avoid applying too high a pressure or pressure difference when liquid is being transferred. Where air and liquid alternate, avoid perforating the stoppers of vials many times with new perforations, change the point of insertion, trap possible aerosols with sterile compresses when the needle is inserted or removed from the vial and bag by holding the tip of the syringe in the compress.

#### *Measures on contamination with cytostatic drugs*

##### *Contamination of the skin*

Flush immediately with lots of water, possibly soapy water.

##### *Splashes in the eye*

Flush immediately with lots of water or sodium chloride 9 mg/ml. Contact an ophthalmologist.

##### *Contamination of floors, benches, etc*

Wipe immediately with disposable cloths. Then wash with soapy water. The disposable cloths should be treated as hazardous waste. Use thick gloves or two disposable gloves on top of one another. Plastic gloves should not be used.

### **Administration of cytostatic drugs**

#### *Administration of cytostatic drugs to patients*

*The person who is to administer cytostatic drugs must have experience of venepuncture.*

*Normally it is the responsibility of the doctor to administer intravenous chemotherapy. If nurses are to administer cytostatic drugs outside hospital, they must be offered training. Nurses who have to had the requisite training must not administer cytostatic drugs.*

The person giving an injection or infusion of cytostatic drugs should use gloves.

Intravenous administration by infusion is the most widely used and safest method of giving cytostatic drugs. Intravenous administration can also be by injection. In practice this means a short infusion with a minibag or a bolus injection with a syringe.

#### *Short infusion with minibag*

This is the most widely used method of administering cytostatic drugs.

The administration takes place in a "closed" system, and it has been shown that the drugs are well tolerated by patients when they are given in this way. The following procedure can be used:

1. Choose a large bore vein, preferably in the forearm. Insert a venous cannula.
2. Apply a compress around the injection site to avoid contamination of the patient's skin.
3. Hang sodium chloride 9 mg/ml (100 - 500 ml) with a Y-set. Let it run in at a rate of approx. 500 ml/30 min, at the same time checking that the fluid is not going extravascularly.
4. Attach the minibag containing the cytostatic drugs to the other branch of the Y-set. The sodium chloride infusion may be stopped temporarily or proceed in parallel with the drug infusion.
5. When the infusion of cytostatic drugs is complete, flush through with the rest of the sodium chloride solution.
6. If several cytostatic drugs are to be given in the same course, using a 4-branch infusion set provides the least risk of contamination. It should be flushed with sodium chloride 9 mg/ml between each cytostatic drug. Alternatively, use a Y-set and change bags after the side branch has been flushed with sodium chloride solution.

#### *Bolus injection with syringe*

This method of giving cytostatic drugs is no longer particularly common, but if it is used a neutral drip (sodium chloride 9 mg/ml) should be hung as described above. Cytostatic drugs are then injected into the rubber sleeve on the infusion set while the infusion is running freely (commonly a simple infusion set). After the cytostatic drug has been injected, flush through with the remainder of the infusion fluid.

#### *Intramuscular injection*

Intramuscular injection can be used for certain cytostatic drugs that are irritating to tissue. Investigate the risks before injection commences. See the manual (3) and the Pocket Catalogue.

#### *Subcutaneous injection*

Subcutaneous injection can be used for cytarabin.

#### *Extravasation of cytostatic drugs*

Some cytostatic drugs are so irritating to tissue that infusion/injection outside the vein (extravasation) can cause serious damage. It is therefore important to observe the patient carefully and to make sure that the injection/infusion is proceeding intravenously as it should.

#### Signs of extravasation

- smarting pain around the injection site
- local swelling
- local inflammation of the skin
- stagnation of the rate of the drip

For more detailed advice and instructions see the handbook (3) pp. 436 - 439 and table p. 452.

#### *Instillation of cytostatic drugs in the bladder*

Some cytostatic drugs can be used for local treatment of bladder cancer. Instillation of a cytostatic drug in the bladder and drainage after the treatment is complete should be carried

out in as closed a system as possible in order to avoid contamination.

Prepare the drug in a partly empty 250 or 500 ml infusion bag, with room for urine when the bladder is emptied. Connect the bag to the patient's catheter using a special bag/catheter connection and force the drug into the bladder. Clamp the catheter off, but keep the bag connected.

After the prescribed treatment time, open the catheter clamp and the solution empties out of the bladder into the bag. Destroy the bag as hazardous waste.

#### *Cytostatic drugs for oral use*

Cytostatic drug preparations for oral uses should be swallowed whole with at least one glass of water. Direct skin contact should be avoided. Tablets should not be crushed or split, capsules should not be opened. See the handbook (3), table p. 542.

## **Waste**

#### *Handling of waste that has been in contact with cytostatic drugs*

Waste from cytostatic drugs includes residues of the drugs and all equipment that has been used in their preparation and administration. Disposable latex gloves must be used when handling waste. The waste is divided between needle buckets or similar and tough plastic bags, e.g. large zipper bags that can be resealed. The air should be squeezed out of the bag before it is closed. All waste of this type should preferably be collected in cardboard boxes that are clearly marked "Cytostatic drug waste" and sent for incineration at high temperature (>800°). The waste should be removed from the workplace as soon as possible.

Where incineration is impossible, large residues of cytostatic drugs, e.g. partly used medicine bottles and courses that have not been administered, should be gathered up, packaged and labelled as stated above and sent to the nearest hospital or pharmacy for destruction. Smaller residues such as infusion sets, empty bags, gloves, empty medicine bottles, and needle buckets should be packed in plastic and disposed of as hazardous waste.

#### *Handling of excretion products from patients*

Urine, vomit and faeces from patients receiving cytostatic drugs can contain drugs in an active form or as metabolites. The amount of a cytostatic drug that is excreted depends on what substance has been given and the size of the dose. Doses given outside hospital are moderate, and it is preferable to have a significant period between each course of cytostatic drugs. Urine, faeces and vomit do not, therefore, normally represent any risk, but staff should use gloves and a mask in the event of possible contact with excretion products from patients who have received cytostatic drugs. Bedpans and urinals must be emptied in a single go. Do not allow urinals and bedpans to remain uncovered.

## **Literature that should be available**

(1) Forskrift om legemiddelforsyning m.v. i den kommunale helsetjeneste (Regulations on the supply of medicines, etc., in local authority health services), put into effect by the Directorate for Health and Social Affairs, 18 November 1987. Amended by order of the Ministry of Social Affairs on 21 January 1991.

(2) Forskrifter om håndtering av cytostatika (Regulations on handling of cytostatic drugs).

Norwegian Labour Inspection Authority, 18 December 1980, with amendments, latest 22 March 1993.

(3) Cytostatica. Medikamentell kreftbehandling (Cytostatic drugs. Medicinal treatment of cancer). Institute for Pharmacotherapy and The Norwegian Cancer Association. 5<sup>th</sup> edition 1994. Obtainable on request from Norsk Medisinaldepot.

(4) Felleskatalog over farmasøytiske spesialpreparater (Pocket catalogue of special pharmaceutical preparations), latest edition. Felleskatalogen A/S, Oslo.

(5) Norsk legemiddelhåndbok for helsepersonell (Norwegian medicines handbook for healthcare staff), latest edition. Norsk legemiddelhåndbok I/S, Oslo.

(6) Kirsten Myhr. Cytostatika. Håndtering og administrasjon (Cytostatic drugs. Handling and administration). 2<sup>nd</sup> edition 1991. Obtainable on request from Pharmacia AS.