Oncology pharmacy

Cytostatics and treatment of cancer
Management of side effects
Compounding

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Cytostatics and treatment of cancer

Surgery
Radiotherapy
Pharmacotherapy

- Conventional chemotherapy
- „Biological“ therapy
- Conjugated molecules
- Hormonal therapy
- Radiopharmaceuticals

Cells, vaccines, and GMOs

Therapy protocols

Conventional chemotherapy

Stops growth/division of cells
Most significant effect in fast growing and dividing cells

- Tumour cells
- Bone marrow cells, hair follicles, mucosa, etc. - side effects

Does not work with slowly growing tumours
Use in non-oncological areas – transplantology and treatment of auto-immune diseases

Conventional chemotherapy – alkylating substances

Agressive substances that react with DNA and disable it by alkylation
Mustard gas derivatives

- Cyclophosphamide
- Iphosphamide
- Busulphan
- Melphalane

Conventional chemotherapy – platinum derivatives

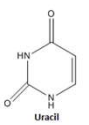
Platinum complexes bind to DNA

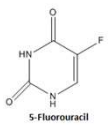
- Cisplatin (renal toxicity, ototoxicity)
- Carboplatin (unique calculation of dose, based on renal functions (eGFR))
- Oxaliplatin (neurotoxicity)

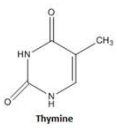
Conventional chemotherapy – antimetabolites

Mimicking the structure of physiological molecules (nucleosides, folic acid)
Replacing them in structures leading to dysfunction

- 5-fluorouracil, capecitabine (oral, prodrug)
- Gemcitabine
- Methotrexate





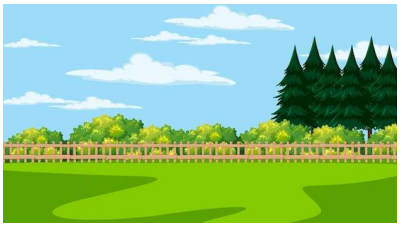


- Cytarabine, fludarabine, trifluridin, pemetrexed

Conventional chemotherapy – plant alcaloids and terpenes

Inhibition of various enzymes essential for the cell growth / division

- Taxanes – paclitaxel, docetaxel, cabazitaxel
- Campthotecins – irinotecan, topotecan, govitecan
- *Vinca* alcaloids – vinblastine, vincristine, vinflunine, vinorelbine
- Podophyllotoxins – etoposide
- *Maytenus* macrolides - emtansine



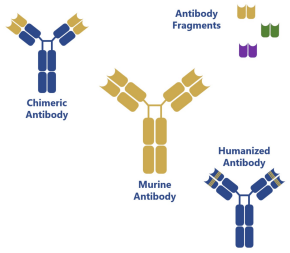
Conventional chemotherapy – bacterial and fungal products and others

- Anthracyclins – doxorubicine, epirubicine
- Bleomycin
- Mitomycin C
- Actinomycin D
- Ozogamicin

- Eribulin
- Trabectedin
- Vedotin

„Biological“ therapy – targeted therapy

Targetted on cancer cells more successfully than conventional chemo
Targetted on receptors on the cancer or supportive cells or on the enzymes inside them that are necessary for growth, division, DNA repairs
Effective only if their target is presented on/in the cells – some kind of testing is often needed
Less side effects than chemo



- Monoclonal antibodies
- „Small molecules“ - orally administered

Targeted therapy – monoclonal antibodies

- Rituximab (since 1997) – against CD20 on B cells (B-lymphoma, autoimmune disorders)
- Trastuzumab, pertuzumab – against Her2 receptors on cancer cells
- Bevacizumab – against vascular endothelial growth factor A – slows down the formation of new veins
- Panitumumab, cetuximab – against epidermal growth factor receptor on colorectal cancer cells

Targeted therapy – small molecules

Kinase inhibitors – against one or more enzymes in signal pathways in cancer cells

- Cyclin-dependent kinase inhibitors
- Vascular endotelial growth factor receptor inhibitors
- Poly ADP ribose polymerase inhibitors

Imatinib (since 2001)
About 30 molecules authorised for use now

„Biological“ therapy – checkpoint inhibitors

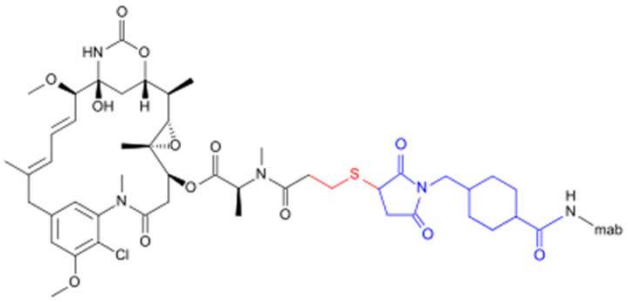
Restore immune system function that the cancer had blocked
Monoclonal antibodies (so far) against various receptors on T cells
Overactivation of the immune system can cause autoimmune disorder in almost any organ or tissue (severe in 1/7 of patients)

- Ipilimumab (since 2011)
- Nivolumab, pembrolizumab, avelumab, cemiplimab, atezolizumab, durvalumab

Conjugated molecules

Monoclonal antibody against a receptor on a cancer cell and conventional chemo are covalently linked
Better targetting, more efficacy, and less side effects

- Brentuximab vedotin
- Inotozumab ozogamicin
- Trastuzumab emtansine
- Trastuzumab deruxtecan
- Sacituzumab govitecan



Hormonal therapy

Breast cancer – 80 % are estrogen-dependent
Prostate cancer – 100 % are testosterone-dependent

Antiestrogen therapy

- Selective receptor modulators – tamoxifen
- Selective receptor degraders – fulvestrant (depot injection)
- Aromatase inhibitors – anastrozol, letrozol, exemestane

Antiandrogen therapy

- Androgen receptor antagonists – bicalutamide, enzalutamide, apalutamide, darolutamide
- Synthesis inhibitor – abiraterone

Hormonal therapy

Gender non-specific antihormonal therapy – gonadotropine releasing hormone agonists
Overstimulation of hormone production disrupts feedback systems, leading to downregulation of this production
Flare effect (increase of hormonal level at the start of the treatment)

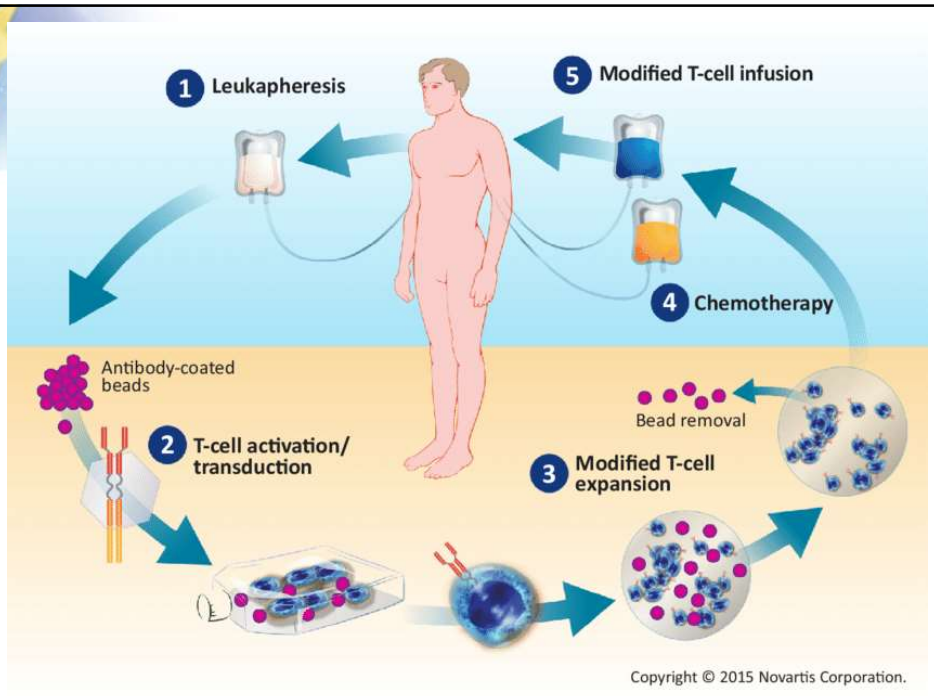
- Goserelin, triptorelin, leuprorelin

Implants or dispersions of biodegradable polymers
1 month to 6 months dosing intervals

Cells, vaccines, and GMOs – CAR-T cells

- Leukocytes are isolated from blood of the patient or a donor
- T-cells are proliferated and stimulated to expand their number
- T-cells are treated with retroviral vector to change their DNA
- Patient undergoes lymphodepletion chemotherapy
- Patient recieves infusion of CAR-T cells

The process has to be performed on-site under GMP conditions (it may be done in a sufficiently equipped pharmacy)
Extremely costly, 100000 euro per treatment



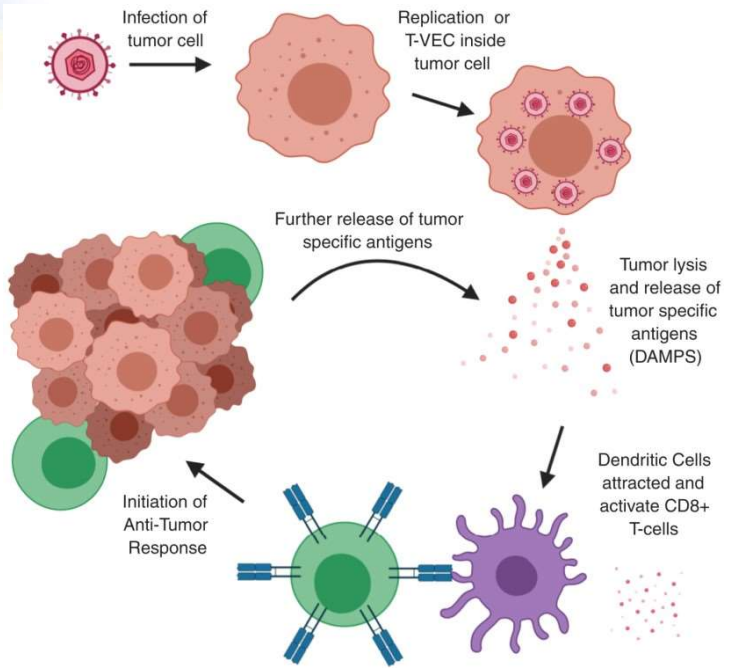
Cells, vaccines, and GMOs – oncolytic viruses

- Herpes simplex virus is genetically modified
- Two genes removed
- One gene added

Virus is unable to reproduce in normal cells, but reproduces in cancer cells, killing them in the process

Virus „persuades“ the host cell to produce granulocyte stimulating factor, attracting the attention of the immune system

Extremely costly, 50000 euro per treatment



Therapy strategies

- Neoadjuvant setting (prior to surgery, aimed to reduce the size of the tumour)
- Adjuvant setting (after surgery, to prevent survival of remaining cancer cells)

- Curative setting (achieving complete remission = patient will be cured)
- Palliative setting (improving the quality of life by slowing down the illness and/or mitigating the symptoms)

Therapy strategies

1st, 2nd, … line of treatment

Treatment protocols following national/international standards

- Monotherapy
- Combined therapy
- Combined chemo
- Chemotherapy+radiotherapy
- Chemotherapy+targeted therapy
- Chemotherapy+immunotherapy
- Immunotherapy+targeted therapy

Dose calculation

- Flat dose
- Dose per bodyweight mg/kg
- Dose per body surface mg/m^2

Studies in 1950s suggested dosing based on body surface to be more effective and safe, mainly in children

Various methods of calculation
DuBois & DuBois (1916) formula most common
BSA = $W^{0.425}$ x $H^{0.725}$ x 0.007184 (W in kg, H in cm, result in m^2)

Way of administration

Intravenous injection/infusion

Intraperitoneal, intravesical, intrathecal, intracardial, intrapleural

Oral

- Take care and pay attention! The drug is handled at home!

Way of administration

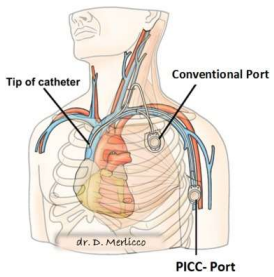
Short-term intravenous protocol – cannula for every day of administration

- Risk of vein damage

Long-term intravenous protocol – PICC (up to 1 year), intravenous port (several years)

- Risk of thrombosis/infection

Type of port



Dose modification

- Due to side effects
- In case of liver or kidney malfunction
- Based on SmPC and clinical trials
- Dose reduction at the first administration (frail patients)

- Dose delay
- Dose reduction (by %)
- Omitting the causing agent in protocols with more drugs

Compounding

Personnel
Occupational health and safety
Rooms and equipment
Aseptic working and its validation
Stability of the preparations

Compounding – personnel

Pharmaceutical personnel

- Pharmacists, pharmacy students
- Pharmacy technicians, pharmacy technicians – trainees
- Pharmacy assistants, residents, interns, etc.
- Pharmacy engineers
- Nurses (e.g. in Greece)

Compounding – personnel

Non-pharmaceutical personnel

- Pharmacy auxilliary staff
- Cleaning staff
- Transport staff

Pharmaceutical and non-pharmaceutical personnel without direct contact with compounding but sharing the premises

Maintenance and repairs

Compounding – personnel

Properly trained and educated
Training plan
Adherence to quality management system
Hazard evaluation

Compounding – personnel

Standard operating procedures

- Written SOPs required wherever hazardous substances are handled
- Description of workplace/activity
- Classification and labelling of hazardous substances
- Hazards for persons and environment
- Protective measures, rules for behaviour, and organisational rules
- Action in case of danger/incident/accident
- Disposal of residues, contaminated materials and devices

Compounding – personnel

Instructing and educating the staff

- Based on their involvement in the process, every staff member has to be instructed and this instruction repeated on regular basis
- Instruction must be documented in writing, identifying date, instructor, instructees, and topic
- Practical simulations (use of protective equipment, training of clean working, incident management) should be included

Compounding – occupational health and safety

Medical check-ups

- Initial
- Follow-up (every 1-2 years)
- In case of suspecting work-related problems

Various legal requirements in particular countries

- Full blood count
- Allergies (i.e. latex)
- Biological monitoring of occupational exposure

Compounding – rooms and equipment

High quality in every step of the process

- Protecting the sterile product from the environment
- Protecting the environment from the hazrdous product

Follows national laws and regulations (even within the EU they are not harmonized)

Compounding – rooms and equipment

General principles

- Appropriate maintenance and upgrading
- Logical workflow and segregation of activities
- Pest control
- Cleaning itself should not be a contamination source
- Special focus on cleaning after maintenance/repairs
- Accessibility for authorized personnel only
- Defining, monitoring and controlling of working and storage conditions
- Cleanliness, orderliness, sufficient lighting

Compounding – rooms

Stock receiving area
Documentation area
Air-lock(s)
Preparation area
Storage area
Production room
Checking and release area

Detailed layout depends on the size of the unit, technical possibilities of the buliding (adaptation x new construction), etc.

Compounding – rooms

Stock receiving area

- Cleanly defined and marked space
- Separation of CMR and non-CMR drugs
- Personnel protecting equipment

Compounding – rooms

Fundamental rules for cleanrooms

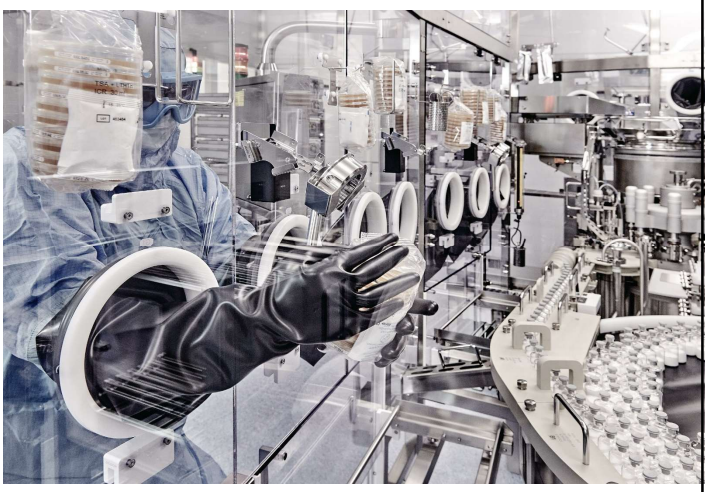
- Contaminants must not be introduced from the outside
- The equipment and processes must not generate or give rise to contaminants
- Contaminants must not accumulate in the cleanroom
- Existing contaminants must be eliminated as fast as possible

Compounding – rooms and equipment

Sources of contamination

- Air
- Surfaces
- Personnel

- Facilities
- Humans
- Tools
- Fluids
- Preparation itself



Compounding – rooms

Workflow
- Personnel
- Material
- Information

The flows should be separated
One-way flows are preferred

Compounding – rooms

Suitable materials
- Stainless steel
- Plastic

- Anti-static
- Washable
- Resistant to disinfectans

Compounding – rooms

EU GMP cleanroom classification
Outdoor urban air – 35 000 000 particles per m^3

	Maximum particles / m^3			
Class	At rest		In operation	
	0.5 µm	5 µm	0.5 µm	5 µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

Compounding – rooms

Airlocks

- Links between zones with different cleanliness rates
- Empty airlock matches the cleanliness of the cleaner room
- Layout depends on cleanroom arrangement (A in B or A in C)
- Air pressure in the cleaner room is 10-15 Pa higher
- Air pressure in the last room before standard environment must be lower than standard pressure to prevent contamination to the outside
- The doors cannot open at both sides at the same time (visual, mechanical or electronical control; must work as emergency exit!)

Compounding – rooms

Gowning and changing rooms – personnel airlocks

- Series of rooms for changing from clothes into cleanroom gowns and back
- Cross-over bench
- Tall wall-mounted mirror
- Stainless steel washbasin with sensor/elbow operated tap (in the clean part)
- Liquid soap dispenser, sensor/foot operated (in the clean part)
- Toilet and shower (in the unclean part)

Compounding – rooms

Preparation room – heating, ventilation and air conditioning (HVAC)

- Supplying airflow in sufficient volume and cleanliness
- Absence of stagnant areas
- Filtering the air through high efficiency particulate air (HEPA) filters
- Conditioning the air to meet temperature and humidity requirements (because of the stability of the products and because of maintaining working conditions)
- Maintaining positive pressurisation

Compounding – rooms

Preparation room – heating, ventilation and air conditioning (HVAC)

- Installed equipment should not affect room conditions
- Air-return grilles should be located near the floor
- Air from the area where CMR drugs are reconstituted should not be recirculated, but released directly to the environment without causing direct danger
- Air from the other areas can be recirculated

In general, cleanroom class B is required for the preparation room
Cleanroom class C or D can be used if properly validated
Depends on local regulations and laws

Compounding – equipment

Actual compounding can be done in:

- Safety workbench for anticancer drugs
- Isolator for cytotoxics
- Biohazard safety cabinet

In any case, cleanroom class A is required

Laws and regulations in particular countries demand usually particular equipment

Compounding – equipment

Proper functioning is guaranteed by:

- Balanced airflow that removes unwanted substances
- Structural integrity (relative in the workbench, absolute in the isolator)

Responsibility for performance testing lies with both the manufacturer and the operator

H14 HEPA filters should be used (filtration efficiency 99.995 %)

Compounding – equipment

Safety workbench requirements

- Downflow velocity ensuring laminar flow (usually at least 0.25 m/s)
- Inflow velocity ensuring proper function (usually at least 0.4 m/s)
- Protection against microbial contamination even under unfavourable conditions

Compounding – equipment

Isolator requirements

- Negative test pressure – no more than 10 % leak volume rate per hour
- Downflow velocity ensuring proper conditions
- Gauntlets or glove/cuff/sleeve system resistant to permeation and penetration by cytostatics
- Construction preventing release of aerosol in the environment if a glove is torn
- Airlocks can not be opened separately

Compounding – microbial contamination

The limits in the table represent average values

Cleanroom	Air sample CFU/m^3	Settle plate CFU/2-4 hours	Contact plate CFU/plate	5-finger glove print CFU/plate
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	Not required
D	200	100	50	Not required

Compounding – microbial contamination

Monitoring follows a plan describing layout of plates and time intervals
Air sampling is recommended quarterly
Settle plates, contact plates and glove prints are recommended much more frequently, up to after every work session (industrial standard)
Cleanrooms classes B to D do not have to be checked so often as A

Two basic rules:

- If everything is OK, prolong the intervals
- If something's wrong, try to improve it and shorten the intervals

Compounding – microbial contamination

Cleaning plan
Rotation of disinfectants

Aseptic technique validation
Monitoring of environment
Sterility testing
Media fill

Compounding – handling of supplies

Suppliers should deliver cytotoxic drugs separately from other drugs
Cytotoxic drugs should be clearly labeled
Cytotoxic x cancer treatment often mixed together
Use of non-sterile gloves and gowns
Wiping vials with NaOH and isopropanole to remove possible contamination is recommended
Secondary packaging can be discarded after receiving (unless necessary for protection from light), note that it is dangerous waste
In case of returning the supplies to the supplier, follow special packaging and labelling procedures

Compounding – protective equipment

Gown
Gloves
Respiratory protection
Hair/beard protection
Protective eyewear
Protective footwear

Compounding – protective gown

General requirements
- Low-lint/lint-free
- Good fit and ergonomy
- Closing down the front

Gown x bodysuit (bodysuit compulsory for cleanroom classes A and B)
Breathability x protection
Disposable x reusable

Compounding – protective gloves

- Sterile for compounding
- Non-sterile for handling before and after compounding

Resistant gloves used for compounding
Note that thiotepa and carmustine permeate all known materials
Double gloving
Regular changes after 30 minutes of work recommended
Breaking glass ampoules – look for holes after preparation

Compounding – respiratory protection and protective eyewear

Not required for standard work – safety workbench or isolator already supply this protection
Required for maintenance and cleaning when the workbench or isolator are opened

- FFP2 mask
- Goggles

Compounding – technical equipment

Standard infusion systems

- Infusion bag or bottle
- Infusion line
- Prefilled with carrier solution to reduce contamination
- In-line filter required in some products
- Residual volume (10-15 ml)

Gravitational infusion line
Pump infusion line
Compatibility between infusion lines and pumps

Compounding – technical equipment

Safety infusion systems

- Infusion bag or bottle
- Infusion line with ports
- Equipped with infusion bag for prefilling and flushing
- Residual volume (1-2 ml)

Proper instructions for nurses concerning administration, safe handling, problem solving, and waste disposal

Compounding – contamination surface monitoring

Most probable route of absorption is skin contact
Preparation room is the safest place in a phamacy/hospital
Critical places – mixing of staff and patients, not respecting clean and unclean areas, waste production, etc.
Large scale monitoring to identify critical places (toilets, infusion stands, office work during administration)
Regular monitoring to verify protective measures and maintain low contamination

Compounding – stability

Saving money and environment – avoiding unnecessary waste

- Stability of reconstituted lyophilized vial
- Stability of prepared infusion bag/bottle/elastomeric pump/syringe

Physical-chemical stability (decomposition, absorption to material)
Microbiological stability (24 hours unless prepared under validated conditons)

Compounding – stability

- Summary of product characteristics
- Internal information of the manufacturer about their stability studies
- Running your own stability study (makes sense in expensive products like monoclonal antibodies)
- Sharing information – papers in journals, stability handbooks and databases (Trissel, Stabilis)

If there are competitors look at stability data when choosing the supplier

Compounding – requirements for prescription

Requirements according to local laws and regulations

- Name, date of birth, gender, unique identification code
- Body weight, height, surface area
- Requesting department
- Name of the drug, preferably INN
- Dose – nominal or absolute or both
- Any dose reduction including justification
- Route and duration of administration
- Type and volume of carrier solution

Compounding – requirements for prescription

Requirements according to local laws and regulations

- Diagnosis to be treated with the prescription
- Date of administration (if presribed beforehand or in multi-day protocols)
- Physician's signature and date of signature

Compounding – requirements for prescription

Prescription can be hand written or electronic
Use of software may help to decrease the risk of error by establishing various controls
The pharmacist should check the prescription and verify its plausibility before processing it further

Ideally, the prescription should be verified for all drugs together, including supporting medications

Masarykův onkologický ústav **NIS MEDEA**

stapro	**Protokol o přípravě aplikace**	**2022/5248_1**
	pacient: **Ing. Štanclová Nikola**	*č. chor.* 3032/2020

umístění: Ambulantní **Přijato:** 05.05.2022 09:41:17
diagnóza: C348 ZN - léze přesahující průdušku nebo plíci
žadatel: MUDr. Bílek Ondřej [tel:6171, ns 010214]
REŽIM: abTXC5, 4. cyklus, 0. část [interval: 124,2 dnů]
Studie
povrch těla: 1,63 m2 Hmotnost:57,5 kg

DEN - Čtvrtek 05.05.2022

účinná látka	ATC	celk. dávka	pumpa	+ čas	doba	poznámky
ATEZOLIZUMAB	L01FF05	1200 mg		+00:00	00:30	Fl/1 [250 ml], Infuse i.v.
BEVACIZUMAB	L01FG01	862,5 mg		+00:30	00:30	Fl/1 [250 ml], Infuse i.v.
Bisulepin	R06AX59	1 mg		+01:00	00:15	Glukóza 5% [100 ml], Infuse i.v
DEXAMETHASON	H02AB02	8 mg		+01:15	00:20	Fl/1 [100 ml], Infuse i.v.
FAMOTIDIN	A02BA03	20 mg		+01:35	00:05	Fl/1 [20 ml], Bolus i.v.
PAKLITAXEL	L01CD01	285,3 mg		+01:40	03:00	Fl/1 [500 ml], Infuse i.v.
ONDANSETRON	A04AA01	8 mg		+04:40	00:15	Fl/1 [100 ml], Infuse i.v.
KARBOPLATINA	L01XA02	568,1 mg		+04:55	01:00	Glukóza 5% [500 ml], Infuse i.v

Compounding – practical tips

Keep the naked spike or needle in your field of vision
Avoid leaving connection points open
Use isopropanole swabs
Avoid unnecessary and rash movements
Only place items you need in the cabinet
Spikes are single use items (1 vial = 1 spike)
Every step requires a plausible reason

Compounding – practical tips

Vials are filled with a slight overfill

- If you work with a needle, you will withdraw more than is labelled
- If you work with a spike or safety device, you are likely to withdraw less due to dead volume

Software is able to deal with these situations

Labeled Size in mL	Mobile Liquids in mL (Percent of Labeled Size)	Viscous Liquids in mL (Percent of Labeled Size)
0.5	0.1 (20%)	0.12 (24%)
1	0.1 (10%)	0.15 (15%)
2	0.15 (7.5%)	0.25 (12.5%)
5	0.3 (6%)	0.5 (10%)
10	0.5 (5%)	0.7 (7%)
20	0.6 (3%)	0.9 (4.5%)
30	0.8 (2.7%)	1.2 (4%)
Greater than or equal to 50	2%	3%

Compounding – practical tips

Reconstitution of lyophylized products

- Gently add diluent and let dissolve or just gently swirl – products containing proteins (monoclonal antibodies, nab-paclitaxel)
- Add diluent and shake vigorously to dissolve (cyclophosphamide)

Compounding – practical tips

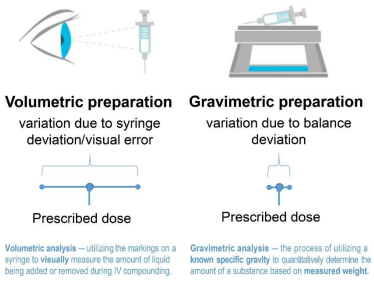
Infusion bag x bottle

- Volume range from 50 to 1000 ml
- Empty infusion bags
- Infusion bags with carrier solution – up to 50 % of additional volume can be added
- Infusion bottles with carrier solution – up to 10 % of additional volume can be added
- Beware of compatibility (saline only, glucose only)

Compounding – practical tips

Volumetric x gravimetric filling

- The software transforms the required dose into a volume of drug concentrate that you need to put in the bag/bottle/syringe
- If gravimetric control is included, you are able check if you added the right amount (weigh before, weigh after, density of the product must be in database)



Compounding – types of products and labelling

Syringe
Infusion bag or bottle
Elastomeric pump
Solution in a bottle for oral treatment

Every item has to be labelled

- Identification of the patient
- Active substance and dose
- Carrier solution, route of administration, total volume
- Storage conditions and expiry date/time
- Name of the pharmacy

Compounding – special formulations

- Atypical dosing schemes in adults, i.e. daily oral administration of drugs othwerise administered intravenously every week
- Administration to patients without oral intake (tube feeding)
- Obtaining doses used in pediatric oncology

Key questions when switching from parenteral to oral dosage form:

- Bioavailability (excludes a lot of drugs)
- Stability (up to 1 month is sufficient)

Compounding – production options for special formulations

Using parenteral drug to make oral solution

Dissolving or suspending tablets in a closed bottle

- Just use the workbench/isolator as usual (etoposide solution, topotecan solution)

Opening capsules or crushing tablets and processing the result in sachets or capsules

- Contaminated dust
- Dedicated area and equipment (in pediatric hospitals)
- Use standard equipment outside cleanroom (e.g. switched off laminar box) and clean extensively (procarbazine capsules, temozolomide suspension)