Dose-banding of chemotherapy agents and its implications for hematology-oncology practice

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Introduction

Definition of dose-banding

Chemotherapy (CTx) doses are clustered into bands of similar dosage levels within a certain range. The mid-point dose of each band represents the respective prescribed dose. This concept allows the preproduction of frequently used doses for CTx substances with adequate stability data.

Advantages

- **Reduction of patient waiting time**
- **Pharmacy workflow optimization**
- Standardised production process
- Increased drug/patient safety
- Cost savings

Methods

Establishing the suitability of CTx substances for dose-banding by:

1. Evaluating ordering frequency and prescription practice

Investigations were based on pharmacy-data (Zenzy - database) of all CTxs used by the Freiburg University Medical Center Hematology and Oncology Department (Med 1) in 2012 and on stability data from the literature. All prescribed CTx doses were banded using the logarithmic method described by Zavery et al.[2] (Fig.1.).

Fig. 1. Logarithmic banding scale

lower level dose- band	prescribed dose for the dose-band	upper level dose-band
54,1	57,1	60,49
60,5	63,9	67,69
67,7	71,5	75,69
75,7	79,9	84,59
84,6	89,4	94,69
94,7	100	105,9
106	112	117,9
118	125	131,9
132	140	147,9
148	156	164,9
165	175	184,9
185	195	205,9

100mg= starting point
next higher prescription dose +11,8%
next lower prescription dose -10,6%

Lower level dose band: mean value of a prescription dose and the next lower prescription dose
Upper level dose band: determined from the consecutive lower level of the next dose band up.

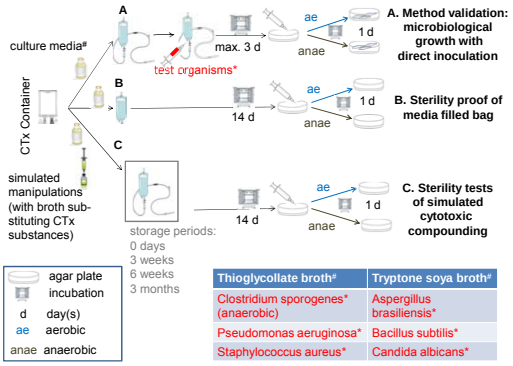
2. Analysis of stability

Based on results of the above evaluations a selection of appropriate CTx substances to undertake stability analyses was made. The maximum storage period was set at 3 months.

Physical and chemical stability tests: For this purpose CTx preparations of Gemcitabine, Carboplatin and 5-FU bolus are made up at the relevant concentrations (within the viable dose bands established). The bags and syringes are incubated at 25°C over the storage period. Quantitative analysis of active ingredient and degradation products are carried out via liquid chromatography at defined storage time points. At all sampling times, a visual inspection of the preparations is carried out for particles and change of colour against a dark and white background. Loss of water is determined by change in weight of the preparations over storage. The pH- is measured initially and at the end of the storage time (Table 1.).

Microbiological stability tests[1]: In order to simulate the worst case scenario, liquid media are used instead of CTx. All manipulations involved in the CTx production process are carried out accordingly. The direct inoculation method is employed for evaluation of sterility (Fig. 2). After 3 months storage time a container integrity test is performed: media filled sample preparations are inserted into bacteria contaminated broth for 1 hour (Fig. 3). After removal, the preparations are incubated for 14 days and examined for microbiological growth.

Fig. 2. Microbiological testing for prolonged sterility

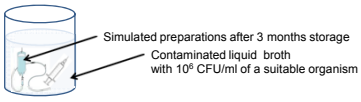


Thioglycollate broth#	Tryptone soya broth#
Clostridium sporogenes* (anaerobic)	Aspergillus brasiliensis*
Pseudomonas aeruginosa*	Bacillus subtilis*
Staphylococcus aureus*	Candida albicans*

Tab. 1. Stability analyses overview

Tests ↓ Time →	week 0	week 1,5	week 3	week 6	week 9	week 12
Quantititv analysis	x	x	x	x	x	x
Particles & colour	x	x	x	x	x	x
Water loss		x	x	x	x	x
pH	x					x
Sterility test	x		x	x	x	x
Container integrity						x

Fig. 3. Container integrity test

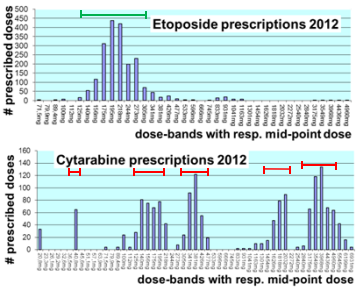


Results

1.1 Analysis of CTx prescribing data: Ordering frequency: "Extended top 15 CTxs"

CTx-data 2012	Total # of CTx preparations (%)	Etoposide	Cytarabine	Gemcitabine	Rituximab	Fluorouracil bolus	Cyclo-phosphamide	Irinotecan	Carboplatin	Cisplatin	Doxorubicin	Bortezomib	Oxaliplatin	Cetuximab	Fluorouracil Baxter pump 48h	Docetaxel	Vincristine	Fludarabine
# preparations for Med 1 inpatient + outpatient data	22310 (100)	2031 (9,1)	1604 (7,2)	1532 (6,9)	1187 (5,3)	1056 (4,7)	1010 (4,5)	854 (3,8)	829 (3,7)	786 (3,5)	752 (3,4)	645 (2,9)	642 (2,9)	552 (2,5)	544 (2,4)	528 (2,4)	454 (2,0)	446 (2,0)
# outpatient preparations (59,3% from total)	13237 (100)	533 (4,0)	37 (0,3)	1338 (10,1)	798 (6,0)	1013 (7,7)	457 (3,5)	811 (6,1)	546 (4,1)	262 (2,0)	331 (2,5)	559 (4,2)	600 (4,5)	526 (4,0)	536 (4,1)	488 (3,7)	240 (1,8)	108 (0,8)

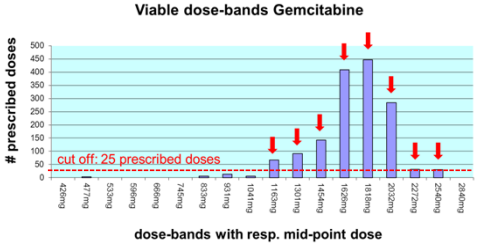
1.2 Dose - frequency distribution



1.3 CTx comparison via dose-banding

2012 data CTx substance	# preparations	stability [3,4] (in weeks)	# production - cycles (per year)	viability limit	# viable dose-bands	# and (%) preparations in viable dose-bands	# preparations per production - cycle
Gemcitabine	**1532**	12	5	25	8	1503 **(98%)**	300
Vincristine	**454**	4	13	65	2	440 **(97%)**	34
Doxorubicin	**752**	17	3	15	15	723 **(96%)**	241
Rituximab (without i.th.)	**1186**	12	5	25	6	1129 **(95%)**	225
Irinotecan	**854**	12	5	25	7	808 **(95%)**	161
5-FU bolus	**1056**	4	13	65	6	972 **(92%)**	75
5-FU 48h Baxter-pump	**566**	16	4	20	7	502 **(89%)**	126
Etoposid-phosphate	**2031**	4	13	65	7	1786 **(88%)**	137
Fludarabine	**446**	5	10	50	4	391 **(88%)**	39
Bortezomib	**645**	5	10	50	3	513 **(80%)**	51

CTx substances are listed in descending order of viability for dose banding .
Only substances with ≥80% of preparations in viable dose bands are shown .

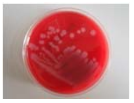


Definitions:
viable dose-band: at least 5 preparations per dose-band and production interval [production interval/cycle = shelf life in weeks]
 # production cycles / year = 52 : stability (weeks)
viability limit = # production cycles x 5

2.1 Sterility testing: validation of the direct inoculation method

Referring to arm **A** of Fig. 2 (methods section)


Aspergillus brasiliensis


Bacillus subtilis


Pseudomonas aeruginosa


Candida albicans


Staphylococcus aureus


Clostridium sporogenes

Conclusions

For implementing the dose-banding concept, a multidisciplinary approach is crucial. Moreover, the careful selection of suitable CTx agents is a key element of introducing dose-banding. Advantages, such as workflow optimization for pharmacy departments and reduction of in- and outpatient waiting time, without compromising patient safety, are convincing arguments for dose banding.

References
1. EDQM: European Pharmacopoeia ,8th Edition, Chapter 2.6.1, Sterility
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4. Thiesen, J.; Krämer, I.: *STABIL-Liste (ADKA)*, 4th Edition, April 2009
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