Model based design of dose-adapted chemotherapeutic regimen under consideration of individual risk of leucopoenia

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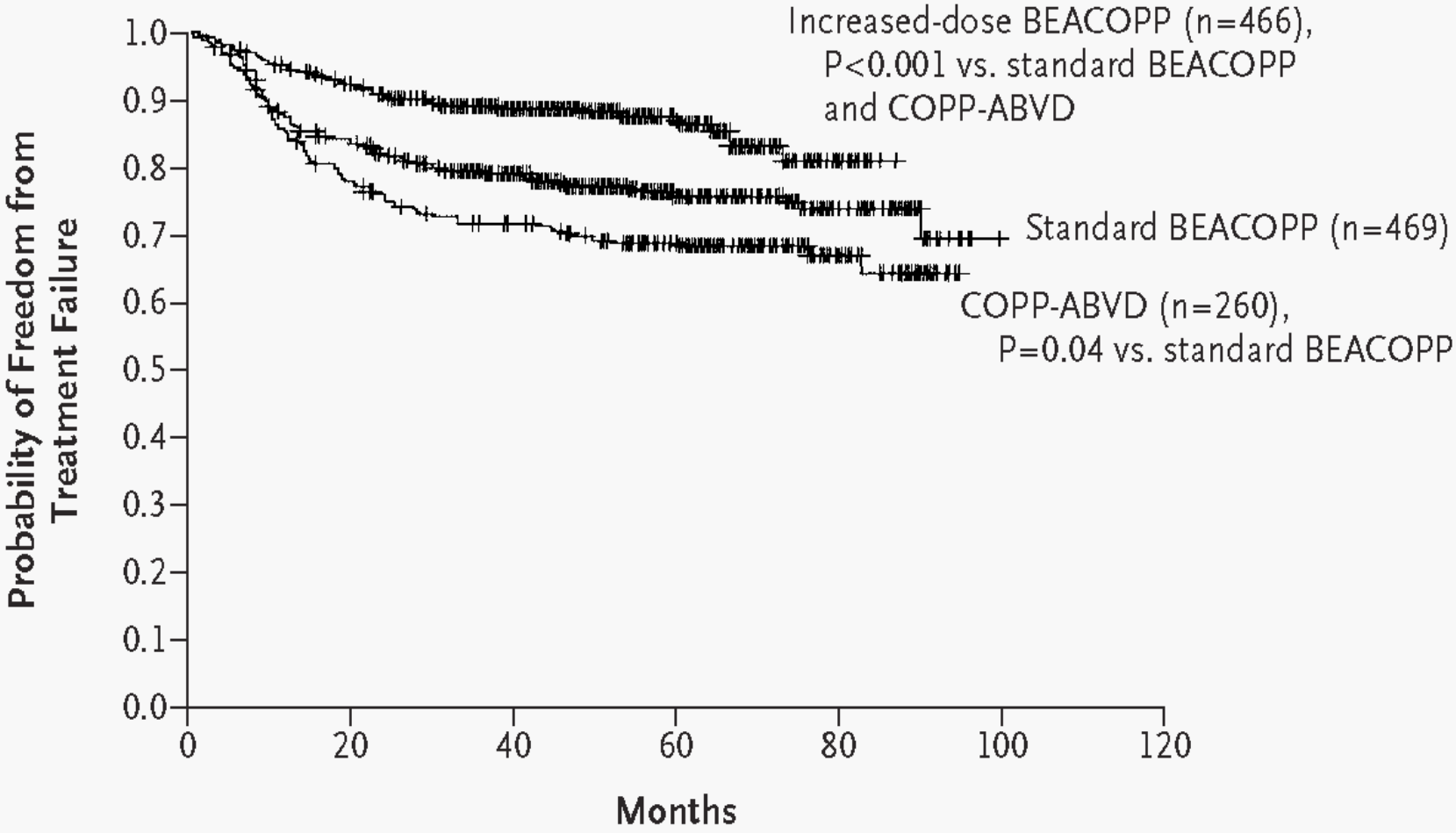
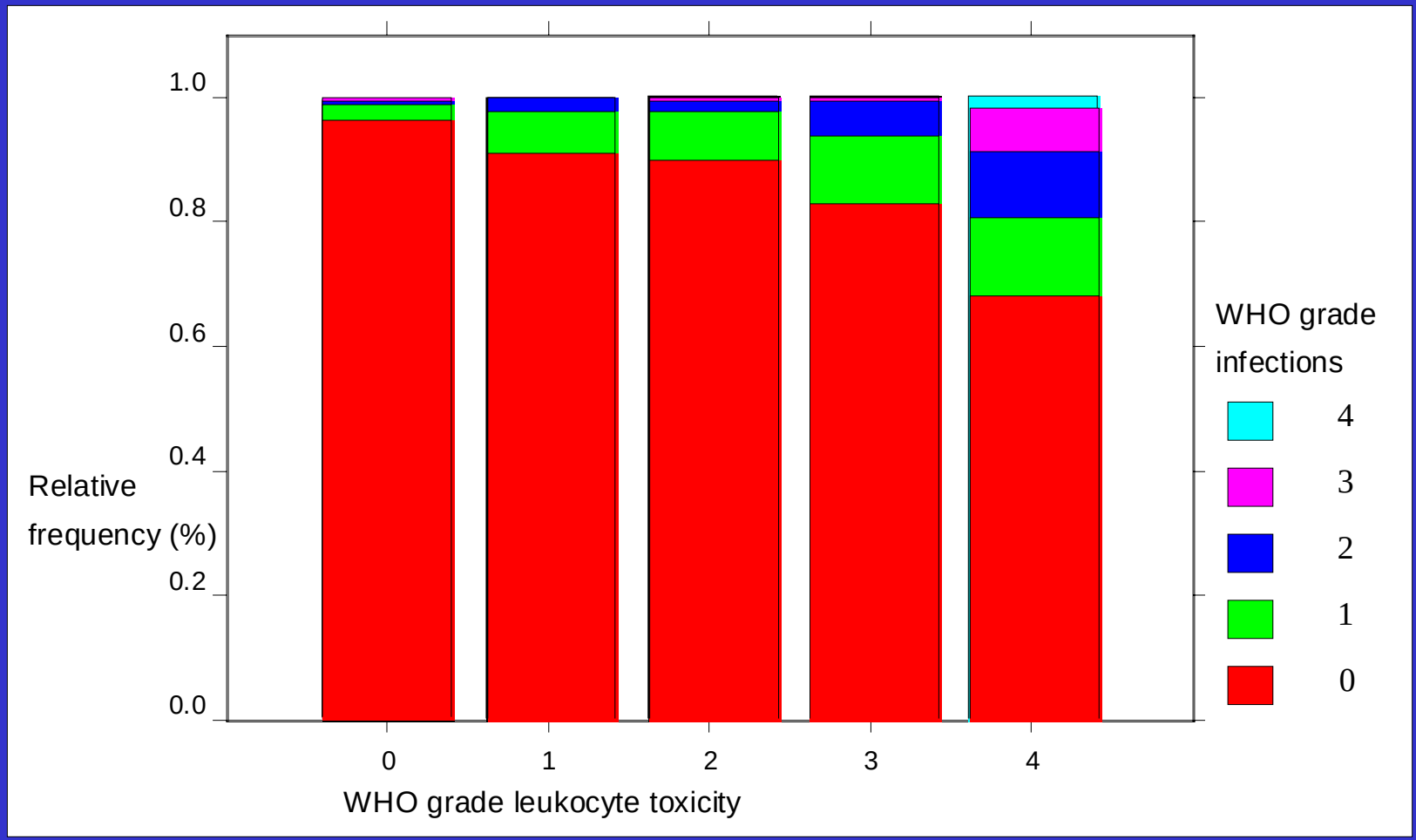
Background: Intensification of chemotherapy (dose, time) can improve outcome e.g. of lymphoma therapy



Diehl V et al; *N Engl J Med 2003 Jun 12;348 (24):2386-95*

Problem: Limitation of therapy intensification by increased leucotoxicity despite of growth factor support (G-CSF)



Data from NHL-B trial, Pfreundschuh et al

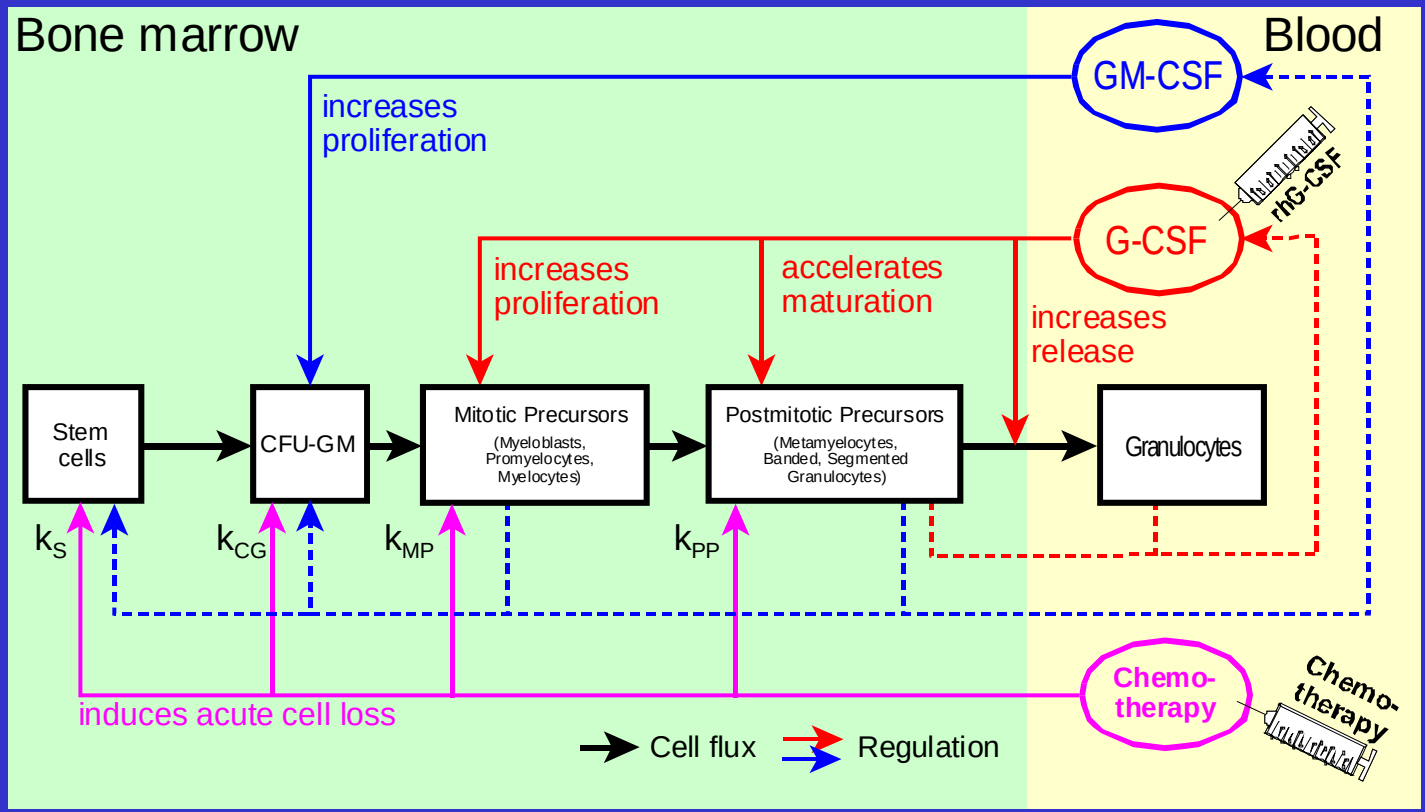
Problem: Heterogeneity of toxicity

- Dose limitation on the basis of a probably small subpopulation with high toxicity
- Low leucotoxicity correlated with worse tumour control in several neoplasias (e.g. Hodgkin‘s lymphoma, Mamma-Ca, germ cell tumour)
- Lack of clinical strategies for dose-escalation in cases of low leucotoxicity during therapy or in case of low predicted risk of toxicity

Motivation for Modelling

- Quantification of the contribution of single components of polychemotherapy to overall toxicity in dependence on individual risk factors
- Estimation of dose-toxicity functions
- Estimation of leucotoxic potential of new chemotherapies prior to clinical trials
- Development of therapeutic regimens adapted for toxicity

Human model of granulopoiesis



Schematic compartment equation

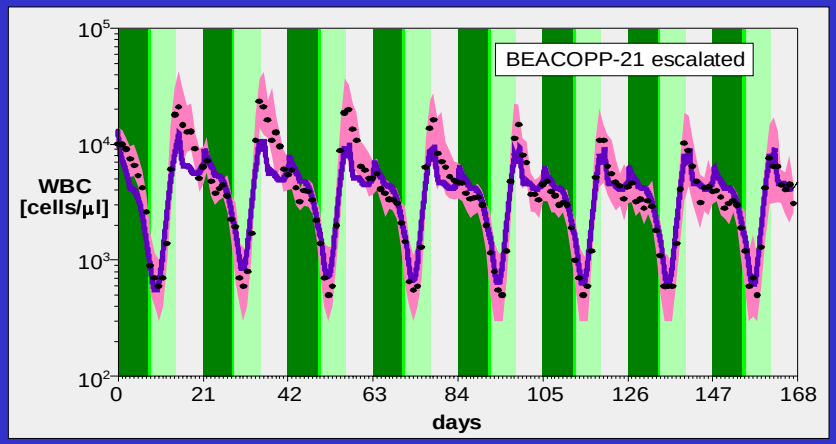
Change of compartment size = amplification(influx)-efflux-cell loss

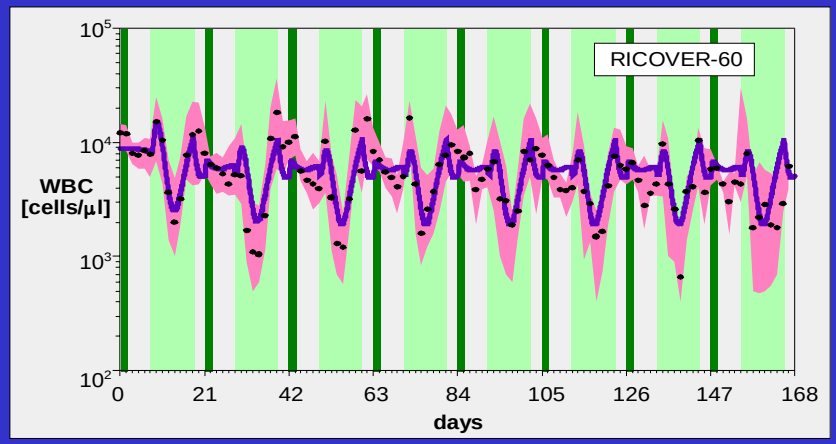
Cell loss = k*compartment size

Assumptions for Chemotherapy Effects

- Instantaneous depletion
- First order kinetic
- Reversibility
- Different drugs in combination damage independently
- Consequence: Chemotherapy effect is characterized by a set of drug dose- and cell stage specific toxicity parameters

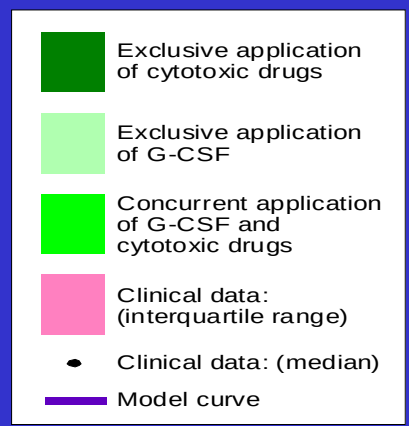
Model based simulation of the time course of leukocytes under several therapies





Estimated toxicity parameters (young patients < 60 years)

	$k_{StemCells}$	$k_{Mitotic\ Precursors}$	$k_{Postmitotic\ Precursors}$
Cyclophosphamide 750 mg/m^2 Doxorubicine 50 mg/m^2 Vincristine 2 mg	0,1775	0,0979	0,0
Cyclophosphamide 1250 mg/m^2 Doxorubicine 35 mg/m^2	0,2139	0,0238	0,0
Etoposide 100 mg/m^2	0,003	0,187	0,0019
Vincristine 2 mg	0,04	0,07	0,0
Procarbacine 100 mg/m^2	0,0063	0,024	0,0015



Model Application: Risk Adapted Dosing for high grade NHL-Patients

- Starting point: CHOP-14 for elderly patients (age>60) from NHL-B trial
- Risk factors for leukopenia
- Assumption: risk factors associated with higher specific toxicity parameters, other parameters constant (e.g. G-CSF response)
- Idea: Homogenize toxicity instead of equal dose

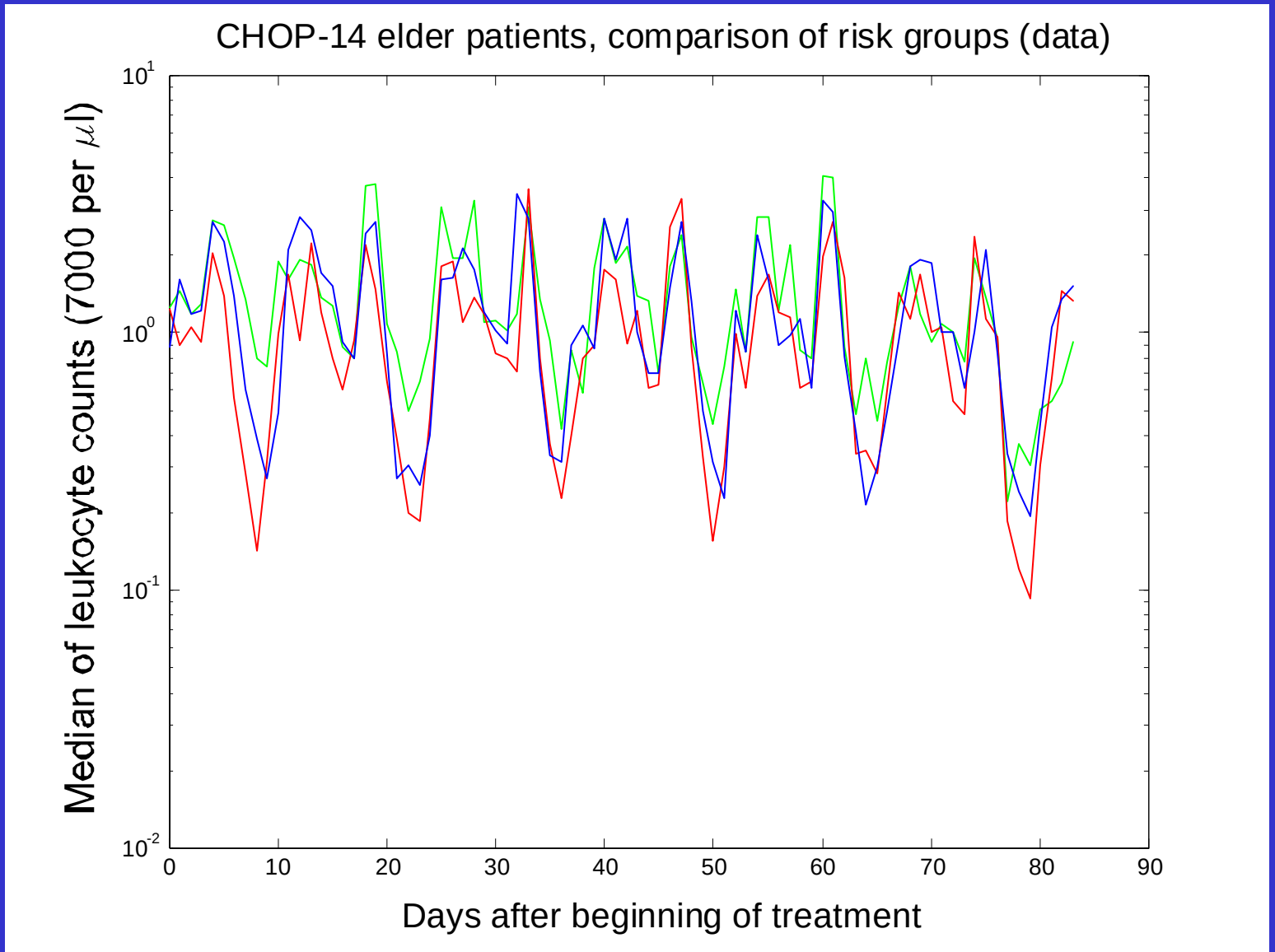
Regimens compared in NHL-B trial

regimen	G-CSF	Cyclophos-phamide	Doxo-rubicin	Vin-cristine	Eto-poside	Pred-nison	cycles
CHOP-21	-	$750\frac{mg}{m^2}$ d1	$50\frac{mg}{m^2}$ d1	$2mg$ d1	-	d1-5	6 d21
CHOP-14	d4-13	$750\frac{mg}{m^2}$ d1	$50\frac{mg}{m^2}$ d1	$2mg$ d1	-	d1-5	6 d14
CHOEP-21	-	$750\frac{mg}{m^2}$ d1	$50\frac{mg}{m^2}$ d1	$2mg$ d1	$100\frac{mg}{m^2}$ d1-3	d1-5	6 d21
CHOEP-14	d4-13	$750\frac{mg}{m^2}$ d1	$50\frac{mg}{m^2}$ d1	$2mg$ d1	$100\frac{mg}{m^2}$ d1-3	d1-5	6 d14

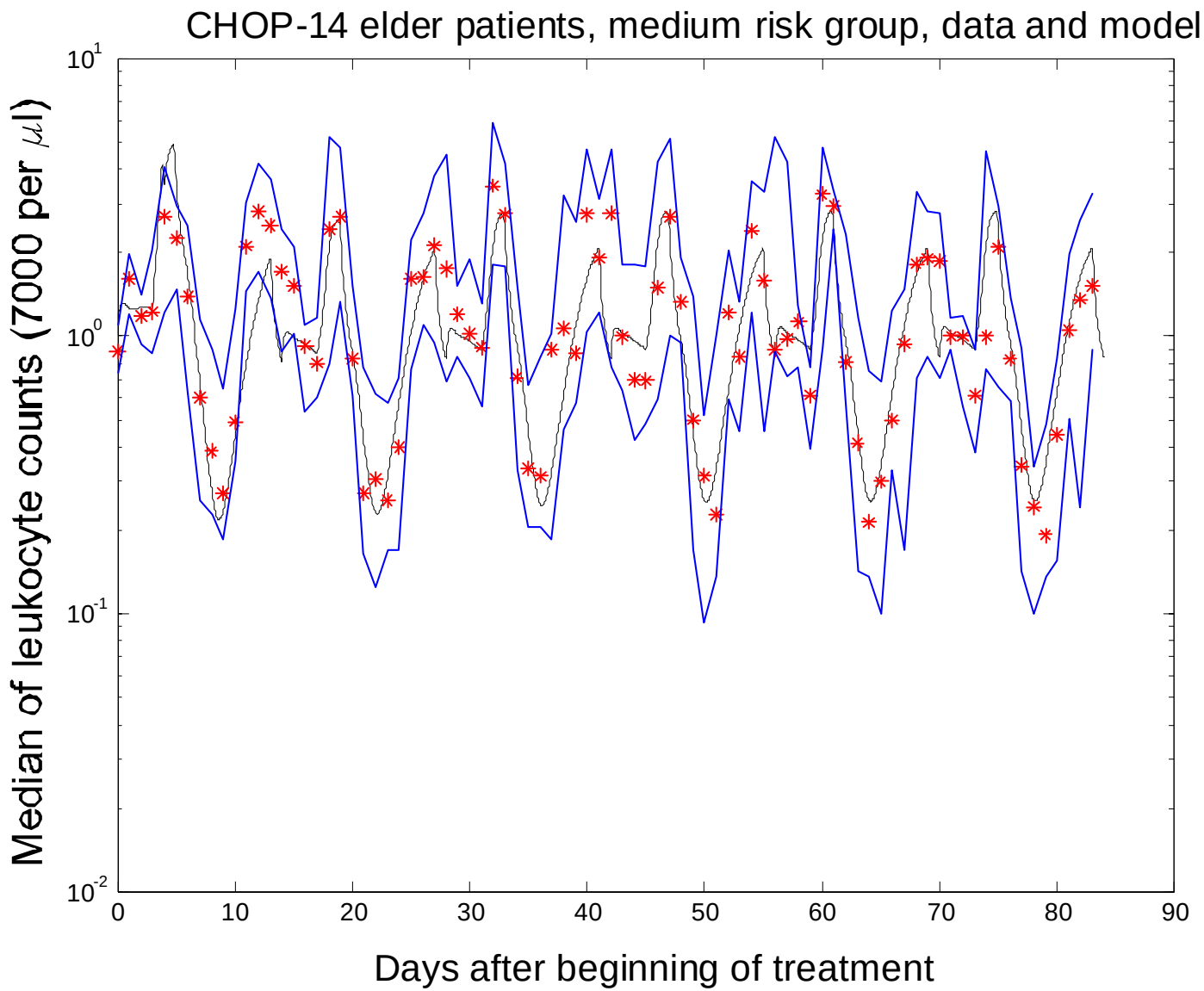
Myelotoxic risk factors for elderly patients

- ECOG performance status>1, female gender, LDH>upper norm value
- Comparable odds

Division of Patients into 3 risk groups (red = high myelototoxic risk, blue = medium risk, green = low risk)



Fitting model to data of risk groups

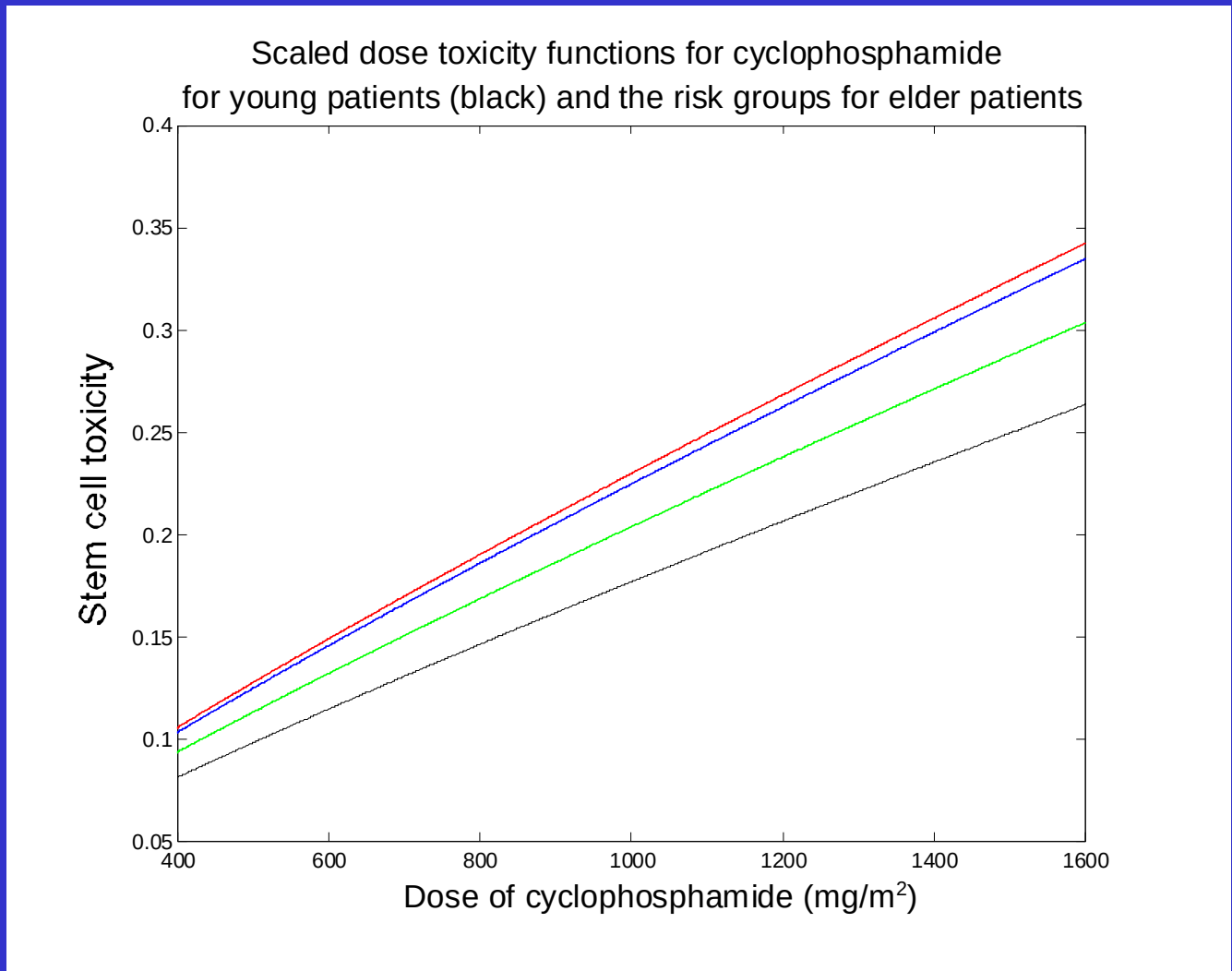


Results of Fitting – Risk specific toxicity parameters for fixed doses of NHL- B trial

parameter	LR	MR	HR
$k_{S\text{-}CHO}$	0.19	0.21	0.22
$k_{PGB\text{-}CHO}$	0.06	0.10	0.2 (>0.1)
$k_{MGB\text{-}E}$	0.004	0.008	0.012

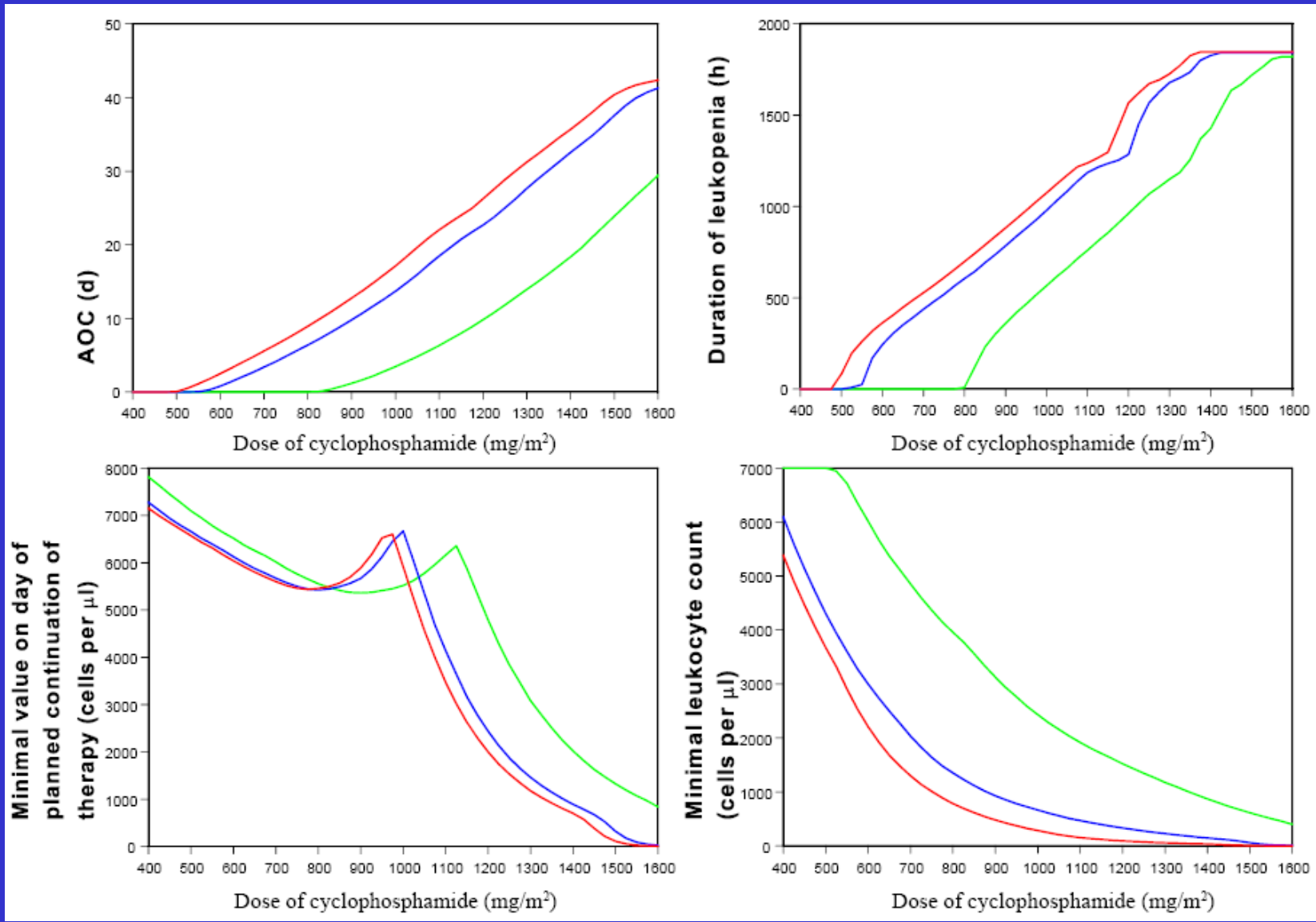
LR=low risk, MR=medium risk, HR=high risk

Dose-Toxicity Functions for Risk Groups (example: stem cell toxicity of cyclophosphamide)



assumption: toxicity ~ dose$^{\text{constant}}$, risk dependent prop. factor

Model predictions for leukopenic characteristics of dose escalated CHOP-14 in dependence on risk group and cyclophosphamide dose

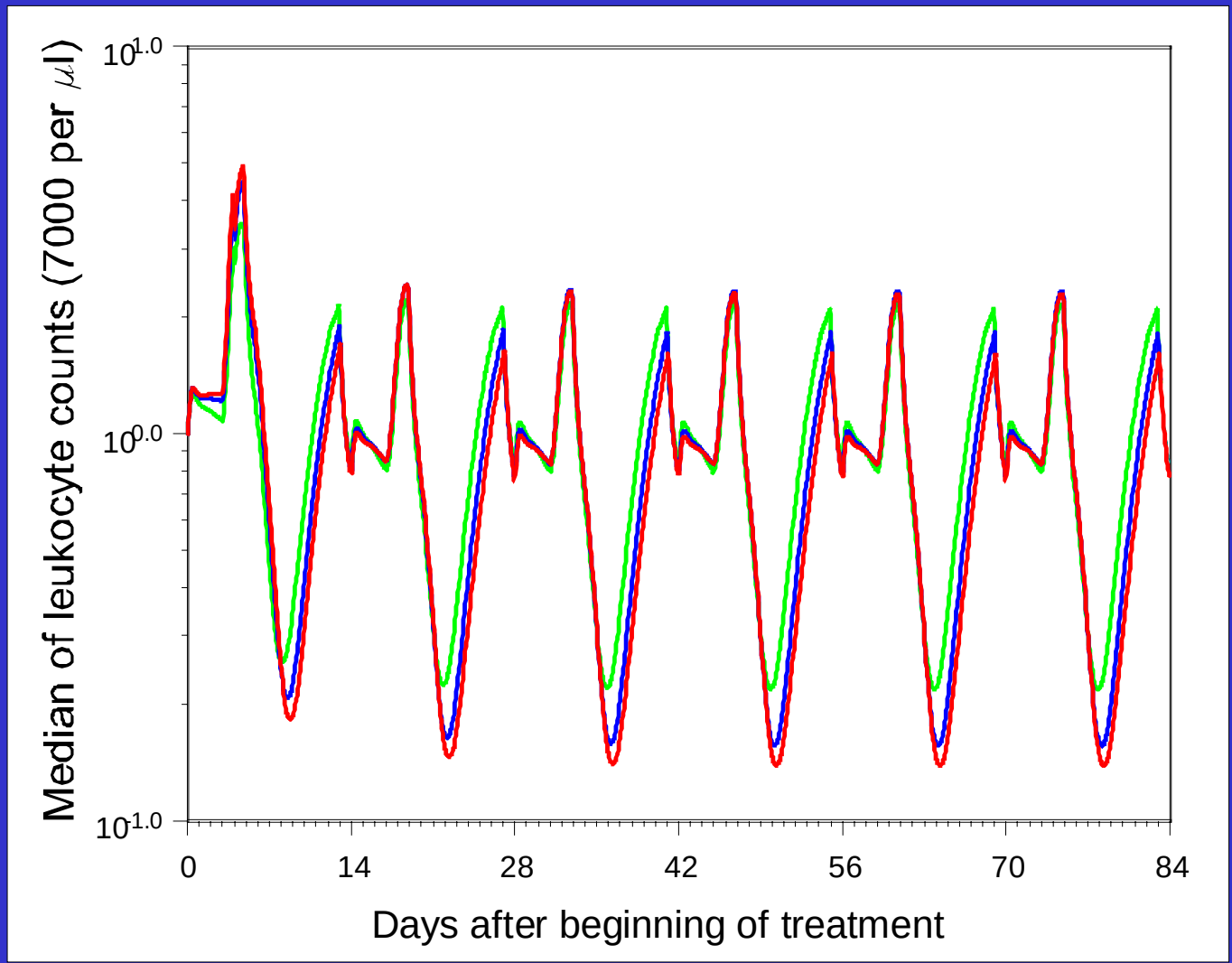


Comparison of leukopenic characteristics for proposed risk-adapted regimens with estimates for clinically approved regimens

regimen	risk group	AOC (h)	duration of leukopenia (h)	minimal recovery value (cells per μl)	minimal leukocyte count (cells per μl)
CHOP-14	LR	0.0	0	5900	4000
CHOP-14	HR	7.4	620	5500	1000
CHOEP-14	LR	4.6	480	5900	1500
CHOEP-14	HR	8.2	650	5500	800
CHOP-21	LR	10.2	1700	4400	2000
CHOP-21	HR	19.6	2100	4100	700
CHOEP-21	LR	18.3	2000	4300	700
CHOEP-21	HR	20.5	2100	4100	600

- Median estimates
- CHOP-14 for HR was used as limit for toxicity
- CHOEP-14 and CHOEP-21 for HR were assessed by clinicans to be too toxic

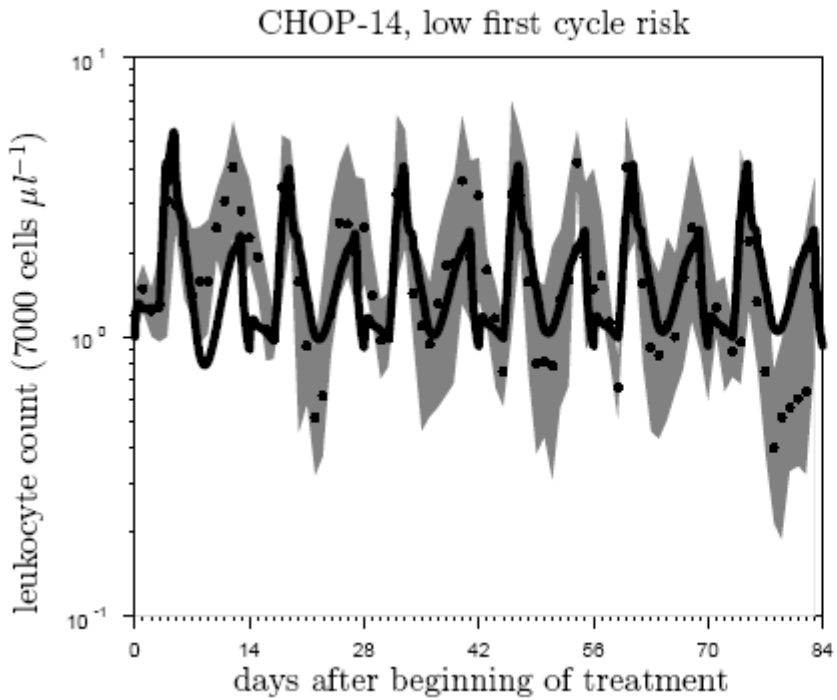
Model prediction for risk adapted CHOP-14 therapy: LR with +300mg/m^2, MR with +150mg/m^2 etoposide, HR standard CHOP-14

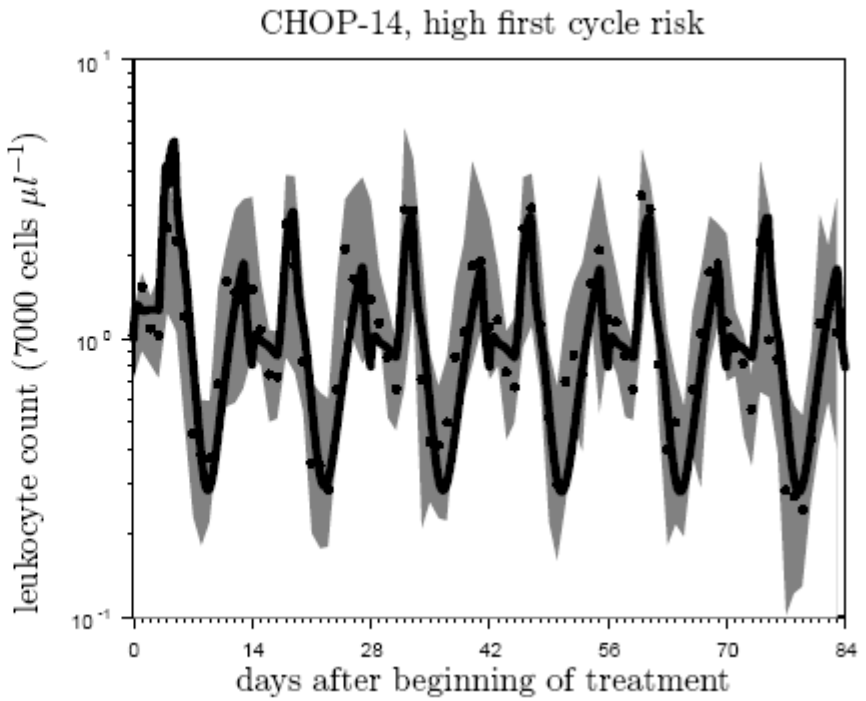


Model predictions for time intensified CHOP regimen
Analysis of G-CSF schedules

regimen	risk group	AOC (h)	duration of leukopenia (h)	minimal recovery value (cells per μl)	minimal leukocyte count (cells per μl)
CHOP-14 (G-CSF d4-13)	HR	7.4	620	5500	1000
CHOP-11 (G-CSF d5-10)	LR	1.9	360	5400	2600
CHOP-12 (G-CSF d5-11)	MR	5.3	580	6700	1500
CHOP-12 (G-CSF d6-11)	MR	4.6	660	6600	1800

Alternative:
Determination of first cycle toxicity as risk marker





Low risk group can tolerate +360mg/m^2 cyclophosphamide without being more toxic than high risk group (model prediction)

Further Possibilities

- Different baseline regimen (different from CHOP-14, G-CSF d4-13)
- Different criteria for equal toxicity, Redefinition of risk groups
- Combination of pre- and intra-therapeutical risk factors
- Dose reduction

Outlook

- Incorporation of further risk factors (e.g. genetic factors of drug metabolism)
- Other diseases (Br-Ca)
- G-CSF derivatives (Pegfilgrastim)
- Individualized G-CSF scheduling
- Comparison with toxicities of other haematological lineages (thrombopenia, anemia)