Dose intensification of chemotherapy: An estimation of hematological toxicity and the effect of different G-CSF administration by model simulation

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INTRODUCTION

Objectives

Model description of polychemotherapy effects on granulopoiesis

Model predictions regarding hematotoxicity of dose intensification or varying growth factor administration schemes

Data

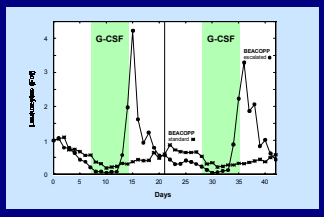
We used mean leukocyte counts from 500 patients of the HD-9 study of the German Hodgkin's Lymphoma Study Group, treated for advanced stage Hodgkin's disease with the BEACOPP protocol.

BEACOPP standard dose (escalated dose) regimen (mg/m²):

bleomycin 10
etoposide 100 (200)
adriamycin 25 (35)
cyclophosphamide 650 (1250)
vincristin 1.4
procarbacine 100
prednisone 40

Number of cycles: 8
Cycle duration: 21 days
Data given in fraction of the initial value (FoI)

G-CSF support (BEACOPP-escalated only): 5µg/kg/d, day7-14



Mathematical model of human granulopoiesis

Cell count dynamics described by differential equations

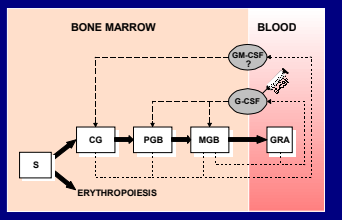
Granulo- and erythropoiesis originate from the pluripotent stem cell compartment (S). Granulopoiesis is governed by two nested feedback loops related to GM-CSF and G-CSF

GM-CSF: stimulates division of committed progenitor cells GFU-GM (CG); it depends on the granulopoietic cell number in the bone marrow

G-CSF: regulates dose dependently the mitotic amplification of proliferative granuloblasts PGB and the transit time of the postmitotic maturing granuloblasts MGB; it depends on a fraction of the most mature MGB and the peripheral granulocytes (GRA)

Effects of G-CSF application

additional mitoses at the PGB stage,
transit time reduction of the MGB cells (early release)



MODELLING OF CHEMOTHERAPY-INDUCED DAMAGES

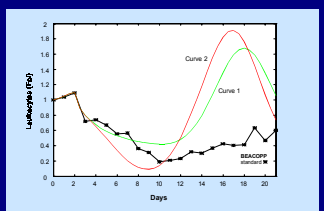
Simulation of chemotherapy effects on granulopoiesis by assumption of acute cell loss

Model curves of peripheral granulopoietic cell counts are compared with BEACOPP data in the first cycle. Acute cell kill is simulated by reduced initial values at time t=0

Initial cell counts given in fraction of the normal values:

	S	CG	PGB	MGB	GRA
Curve 1	0.001	0.001	0.5	0.7	1
Curve 2	0.001	0.001	0.001	0.7	1

The model results show that acute cell loss alone is not sufficient to explain the observed behaviour of granulopoietic recovery



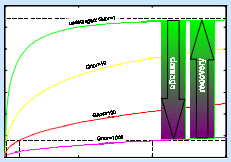
Additional functional damage: reduced proliferative capability

Assumption: Impaired cellular mechanisms (microenvironment included) lead to a transiently reduced mitotic responsiveness to growth factor stimulation

In the model, the defectiveness is described by a transient change of the normal dose-response characteristic of the mitotic amplification of PGB cells. This change is quantified by the parameter

Gnor: G-CSF level necessary for normal amplification $A_{nor}=2^m$ (m=4 mitoses) of PGB cells

Gnor (given in fraction of the normal G-CSF level, FoN) is used as damage parameter



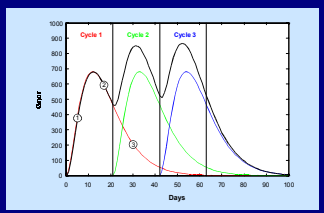
Cycle-dependent damage pattern described by *Gnor*

① Initial increase at the beginning of the cycle: damage

② Decrease after reaching a maximum value: recovery

③ Recovery phase continuing into subsequent cycles: residual damage

Assumption: Cycle-specific damage patterns superimpose in an additive way over subsequent cycles (black curve). Residual damages lead thus to increasing peaks according to the observable accumulation of hematological toxicity



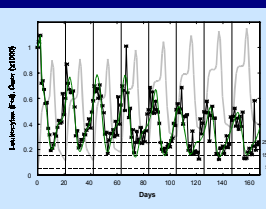
Simulation BEACOPP21 standard

Comparison of the model curve (green) with the observed leukocyte counts of BEACOPP standard dose (✱) over the full therapy duration (8 cycles, each 21 days)

Damage curve Gnor (gray) indicates increasing accumulation of toxicity after the third cycle which corresponds to the decreasing leukocyte nadirs

Simulation technique

step 1: choosing a suitable damage curve Gnor in the first cycle
step 2: continuing the Gnor curve to an 8-cycle damage pattern with a period of 21 days
step 3: adjusting residual damages in the cycles to describe the peak/nadir behaviour observed in the data



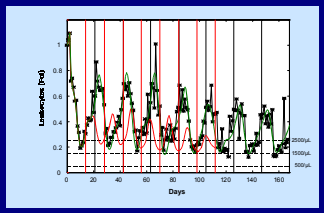
MODEL PREDICTION FOR DOSE INTENSIFICATION BY SHORTENING OF CYCLE DURATION

Model prediction for BEACOPP14 standard

Dose intensification in BEACOPP14 is achieved by shortening the cycle duration from 21 to 14 days. The leukocyte dynamics of BEACOPP14 (red) is predicted by shortening only the cycle duration to 14 days without changing the damage pattern used in the BEACOPP21 simulation (green, ✱) .

Results:

- nadir counts are not lower than with BEACOPP21
- there is no essential increase in the duration of leukopenia in subsequent cycles
- BEACOPP14 standard is therefore feasible without G-CSF support
- Note: application of the cytostatic drugs coincides with the predicted leukocyte nadir phases without adverse effects on further dynamics

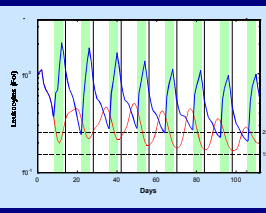


BEACOPP14 standard without and with G-CSF support

Model simulation curves for BEACOPP14 are shown without (red) and with (blue) additional G-CSF application (cycle days 8-12, green bars)

Effects of G-CSF administration:

- clear elevation of the nadir counts
- more rapid recovery
- cycle beginning outside of the nadir phases



MODEL PREDICTION FOR VARYING TIMING SCHEDULES OF G-CSF ADMINISTRATION

Effect of G-CSF administration on the leukopenic phase

BEACOPP escalated data, cycle duration 21 days, G-CSF administration during cycle days 7-14, were simulated

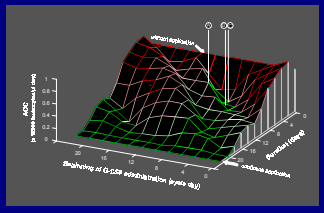
The damage pattern obtained was used to perform simulations with varying timing schedules of G-CSF application

The G-CSF effect was quantified by the area, defined by the 1500 leukocyte/µL-line and the model curve below this threshold (AOC)

The surface diagram shows the AOC for varying beginnings and durations of G-CSF applications:

- AOCs with G-CSF administration (duration>0) are generally lower than without (duration =0)
- there are considerable differences in the efficacy of the application timing
- A most 'economical' region can be found (beginning days 4-8, duration 4-8 days)

Special locations (A), (B) and (C) in the 'economical region' are discussed in the next panel

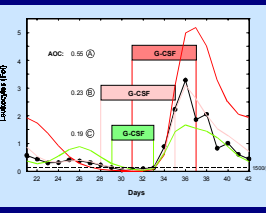


Comparison of three similar G-CSF administration schedules

Location (A): beginning cycle day 10, duration 6 days
Near the economical region. The late G-CSF support leads to an early drop below the 1500 leukocytes/µl threshold and subsequently to a big ineffective overshoot of the model curve (red line)

Location (B): beginning cycle day 7, duration 7 days
In the economical region. It corresponds to the G-CSF administration scheme applied in the BEACOPP escalated protocol (data of the second cycle and model curve indicated by ● and the pink line, respectively)

Location (C): beginning cycle day 8, duration 4 days
In the economical region. Administration scheme with the greatest efficacy and a minimal overshoot (green line)



CONCLUSIONS

Based on white blood cell data of patients treated for Hodgkin's disease a mathematical model developed which allows to estimate the effects of chemotherapy on granulopoiesis. Predictions of the leukocyte dynamics are made for a chemotherapy regimen in which dose intensification is achieved by shortening of cycle duration. Additionally, optimal timing schedules for supportive G-CSF application are proposed. The present analysis provides an example that simulation models may be used as estimation and optimization tools for the discussion of chemotherapy improvement.