Model based optimization of G-CSF scheduling in multicycle chemotherapy

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Objective

To develop a simulation model of human granulopoiesis to optimize cost-effectiveness of G-CSF support during intensified chemotherapies.

Problem

G-CSF is widely used in intensified chemotherapy regimen to mitigate neutropenia. Timing schedules of G-CSF in these regimen is often fixed and do not account for heterogeneity of hematotoxic response between individuals. Strategies for optimal timing of G-CSF support with respect to a cost effective use have rarely been developed so far. Optimal timing of G-CSF administration should produce minimal neutropenia by a minimal amount of G-CSF used.

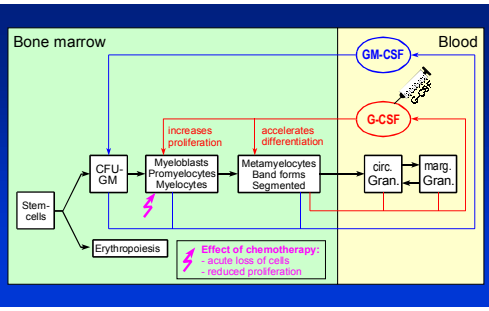
Model of human granulopoiesis

Model properties:

Granulopoietic cell stages are described by compartments which are connected by cell fluxes

Growth factor mediated feedback loops regulate cell production (by affecting amplification and maturation time)

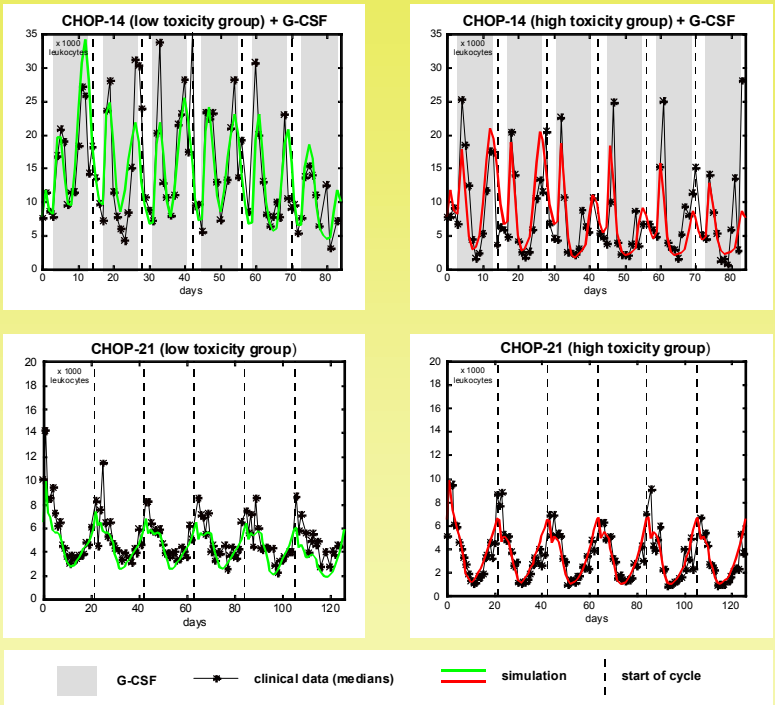
Effects of G-CSF treatment are described independently from effects of chemotherapy



Simulation of granulopoiesis during multicycle chemotherapy

Fit of simulation to clinical data (CHOP-regimen, 21 and 14 days cycle duration)

Model parameters (short and long term effects of chemotherapy) are adjusted by fitting simulation curves to clinical data



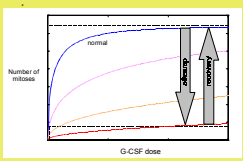
Assumptions for effects of chemotherapy

Short term damage:

Acute loss of cells at the beginning of each cycle (administration of drugs)

Long term damage:

Temporary decrease in mitotic responsiveness of granuloblasts to the G-CSF stimulus (see figure ➔)



Clinical data

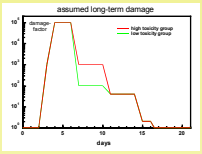
Clinical data (time course of leukocytes during chemotherapy) were taken from:

NHL-B trial (prospective multi-center trial for intensified treatment of high-grade Non-Hodgkin-Lymphoma): *CHOP-14, CHOP-21, CHOEP-14, CHOEP-21*

HD-9 trial (prospective multi-center trial of the German Hodgkin's Study Group for treatment of advanced stages of Hodgkin's disease): *BEACOPP-21-esc*

To consider large interindividual variation in hematotoxicity, patients were divided retrospectively into two subgroups (lower and upper third of a rank statistic attributing a score of cumulative toxicity to each patient adjusted for given dose).

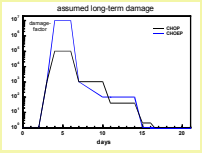
Results



Simulation of CHOP regimen (21 and 14):

Clinical data of CHOP-21 and CHOP-14 (plus G-CSF support) regimen can consistently be described with an identical set of parameters.

These parameters are different for the two subgroups representing different hematotoxicity.



Simulation of CHOP vs. CHOEP:

The additional effect of Etoposide can be described by an increased short and long term damage. However, for both CHOEP-21 and CHOEP-14 identical parameters are assumed.

Simulation of granulopoiesis during chemotherapy assuming different timing schedules of G-CSF

Method of simulating different G-CSF schedules

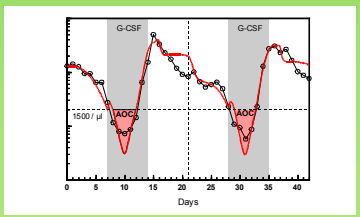
Different timing schedules of G-CSF administration are simulated by varying the following two parameters:

1. day of beginning of G-CSF application after begin of cycle
2. duration of G-CSF application (days)

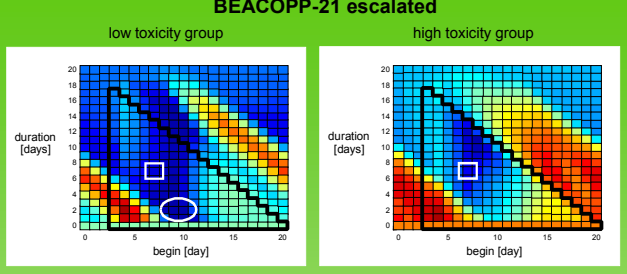
Model parameters for short and long term damage adjusted to clinical data are kept constant for all simulated G-CSF schedules (effects of G-CSF are simulated independently from effects of chemotherapy)

For each schedule, an AOC is calculated which represents the area between the simulation curve and a clinically relevant threshold of 1500 leukocytes / µl (see figure below).

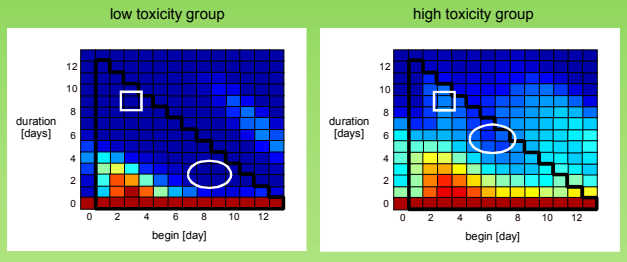
Schedules which predict the same or smaller AOC (compared to AOCs of schedules currently being used) with shorter treatment duration are defined to be more cost-effective.



BEACOPP-21 escalated



CHOP-14



Conclusions

① Effects of different chemotherapy regimen can be comprehensively described with our current model of human granulopoiesis.

② Two major effects of chemotherapy on granulopoiesis have to be assumed to explain clinical data:

1. Short term damage: Acute loss of cells
2. Long term damage: Reduced responsiveness of proliferative cell stages to the G-CSF stimulus

③ G-CSF scheduling might be improved by shorter duration of administration without negative effect on neutropenia for subpopulations of patients.

④ Further analysis of prognostic factors for hematotoxic reaction are needed to identify these subpopulations.

⑤ Further clinical investigation are needed to validate our model predictions.

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