A mathematical model of human granulopoiesis to identify optimal G-CSF scheduling during chemotherapy

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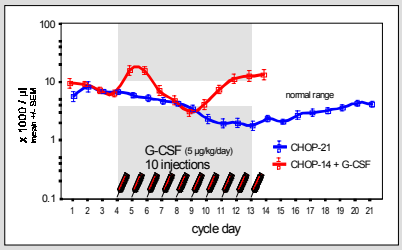
Background

G-CSF permits time-intensification of conventional chemotherapy by improving granulopoietic recovery.

Example: Time course of white blood cell counts (WBC) in patients with aggressive Non-Hodgkin's-Lymphoma during 3-weekly CHOP therapy without G-CSF assistance ("**CHOP-21**") versus 2-weekly CHOP therapy with G-CSF assistance ("**CHOP-14**").

Clinical data of approximately 250 patients from the "NHL-B" trial of the DSHNHL:



Problem

G-CSF considerably **increases costs** of intensified chemotherapy regimens.

The identification of cost-effective application schedules for G-CSF leads to an **optimization problem**: The duration of administration (e.g. number of injections) should be as short as possible (**costs**) and as long as necessary to achieve sufficient granulopietic recovery to allow chemotherapy intensification (**effectiveness**).

The optimization of G-CSF administration by systematic clinical testing of many different injection schedules is highly expensive and time-consuming.

Specific Objective

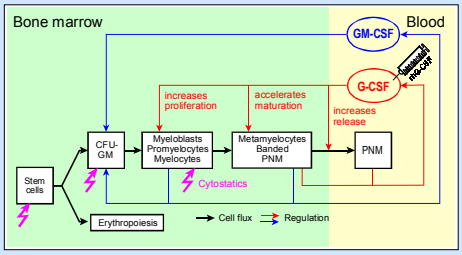
Identification of a cost-effective G-CSF administration schedule during 2-weekly CHO[E]P chemotherapy for consecutive prospective clinical evaluation.

Approach

The time course of leukocyte count in the peripheral blood during chemotherapy and G-CSF administration is simulated by a **computerbased mathematical model of human granulopoiesis**.

Predictions of leukocyte time courses are made for 2-weekly CHO[E]P therapy with different administration schedules of G-CSF (varying begin and number of injections).

Model of human granulopoiesis



Model properties and assumptions

Human granulopoiesis is described by a system of concatenated compartments which respresent the different stages of cell development.

The population dynamics of cell stages are described mathematically by ordinary differential equations (considering specific cell kinetic parameters, e.g. cell division rates, mean transit times)

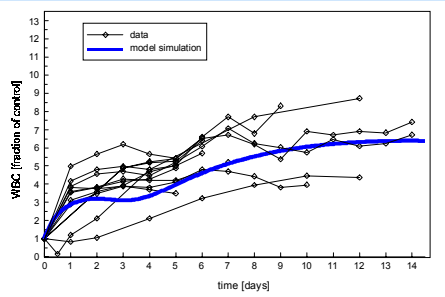
The system is governed by cytokine driven negative feedback loops (G-CSF, GM-CSF)

G-CSF effects: Dose dependent (1) increase of proliferation of mitotic precursors, (2) acceleration of post-mitotic maturation, (3) increase of mature cell release from bone marrow to blood.

Effects of chemotherapy: Acute loss of cells in the stem cell, CFU-GM and proliferative precursor compartment.

Simulation of G-CSF

Determination of the G-CSF-specific model parameters by fitting model simulations to clinical data (time course of leukocytes during repeated daily injections of G-CSF).

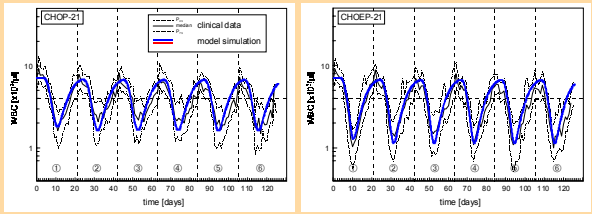


Simulation of granulopoiesis during chemotherapy

Step 1:

Simulation of CHO[E]P-21 (without G-CSF)

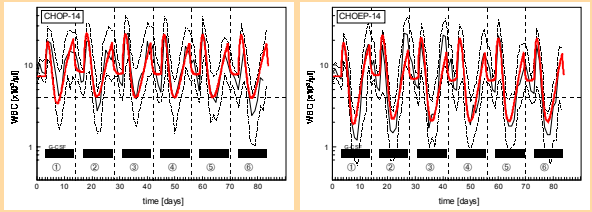
Determination of the "CHO[E]P"-specific cell damage (i.e. model parameters of chemotherapy effects) by fitting model simulations to clinical data from the NHL-B trial.



Step 2:

Simulation of CHO[E]P-14 (with G-CSF)

Modification to step 1: Additonal simulation of G-CSF administration over 10 days (days 4-13) and shortening of cycle duration from 21 to 14 days.

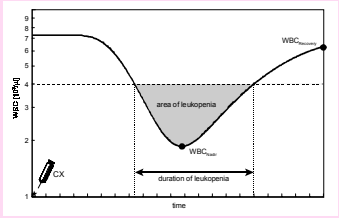


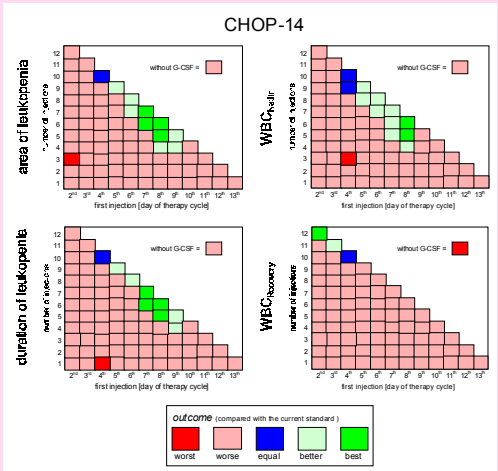
Simulation of different G-CSF administration schedules

The effects of different G-CSF administration schedules on WBC profiles are simulated by systematic variation of the begin and the number of injections.

The severity of leukopenia is judged by:

- *Area of leukopenia* (area over the model curve and under a cinically relevant threshold of the leukocyte count)
- *Duration of leukopenia* (time under threshold)
- *Nadir* (lowest value)
- *Recovery* (WBC on last day of cycle)





Result (model prediction): *G-CSF administration from day 8-12 (= 5 injections)* leads to a more favourable WBC profile than the current schedule.

Conclusion

Based on our model results we performed a pilot study to evaluate the safety and feasibility of the proposed 5-day scheduling: A first interim analysis of 14 patients showed that, although observed leukopenia was more severe than predicted by the model, the schedule did not jeopardize time-intensification (sufficient granulopoietic recovery was achieved within the planned cycle duration of 14 days) and that there were no signs of an increased infection rate as compared to the 10-day scheduling.

Limitations of the model

Model predictions are limited to populations of patients, no predictions for individual patients on the basis of individual prognostic factors for hematotoxicity can be made so far.

Until now, no pharmakokinetic properties of G-CSF are taken into account.

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