A mathematical model of human granulopoiesis to identify economic G-CSF scheduling during 2-weekly CHOP chemotherapy

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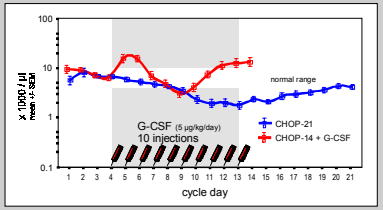
Background

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

Example: Time course of white blood cell counts in patients with high grade 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 demand for a cost-effective application of 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 time-intensification of chemotherapy (**effecteness**).

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

Method

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 CHOP therapy with different administration schedules of G-CSF (varying begin and number of injections).

Objective

Identification of a cost-effective G-CSF administration schedule during 2-weekly CHOP chemotherapy for consecutive prospective clinical evaluation.

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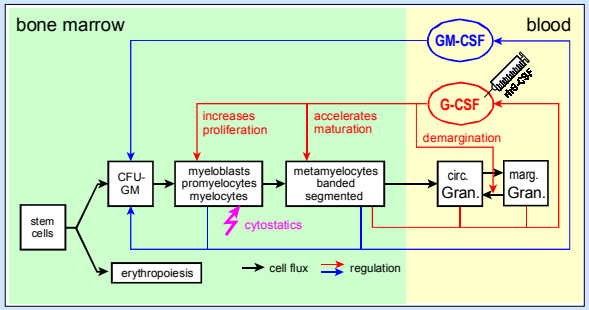
Model of human granulopoiesis



Model properties and assumptions

Representation of human granulopoiesis by a system of concatenated cell compartments (connected by cell flux rates)

Description of the population dynamics of different cell stages on the basis of influx and eflux rates and specific cell kinetic parameters (e.g. cell division rates, mean transit times)

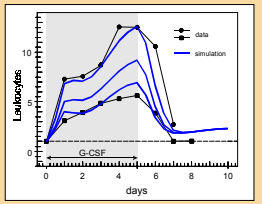
Cytikine driven regulation of cell demand (G-CSF, GM-CSF)

G-CSF effect: Dose dependent (1) increase of proliferation of mitotic precursors, (2) acceleration of post-mitotic precursors, (3) demargination of granulocytes bound to the vessel walls.

Effect of cytostatics: Acute loss of cells and a temporary reduction of the responsiveness of mitotic precursors to the G-CSF stimulus.

Simulation of G-CSF

Determination of the G-CSF-specific model parameters by fitting model simulations to clinical data (time course of leukocytes during daily injections of G-CSF over 5 days).



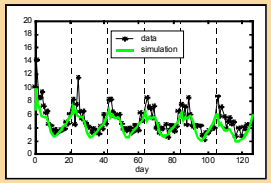
(Schmitz *et al*, Exp Hematol, 1993)

Simulation of granulopoiesis during chemotherapy

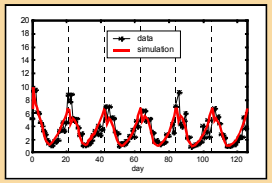
Step 1: Simulation of CHOP-21 (without G-CSF)

Determination of a "CHOP"-specific effect pattern (i.e. model parameters of chemotherapy effects) by fitting model simulations to clinical from the NHL-B trial.

patients with low toxicity



patients with high toxicity

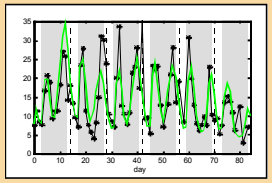


To allow for the heterogeneity of hematotoxicity within the study population, patients were divided into two groups with different severity of hematotoxicity using a retrospective toxicity score.

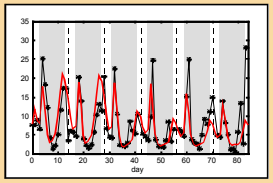
Step 2: Simulation of CHOP-14 (with G-CSF)

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.

patients with low toxicity



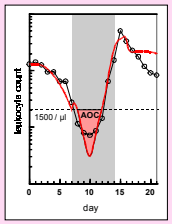
patients with high toxicity



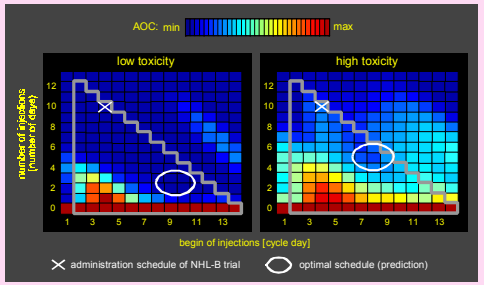
Result: Good agreement of predicted and observed time courses of white blood cell counts.

Simulation of different G-CSF administration schedules for CHOP-14

On the basis of the above model results (determination of parameters) the effect of different G-CSF administration schedules on the time course of leukopenia is simulated (varying systematically the time of begin of injections and the number of injections).



The severity of leukopenia is defined by an "AOC" (area over the model curve, underneath a cinically relevant threshold of the leukocyte count).



Model prediction for a more cost-effective G-CSF administration schedule, which has an "AOC" not larger than during the 10-day administration schedule of the NHL-B trial and which requires less injections:

G-CSF administration from day 8-12 (= 5 injections)

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.

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