Identification of cost-effective timing schedules for G-CSF administration during chemotherapy by computer simulation of granulopoiesis

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Background

- Moderate dose-intensification of chemotherapy can be realized by G-CSF support to mitigate neutropenia
- Scheduling of G-CSF is fixed in most regimen and intra-individual heterogeneity of hematotoxicity is neglected
- Due to its high costs, G-CSF support increases overall costs of dose-intensified regimen considerably
- In face of increasing costs, strategies need to be developed to use G-CSF more cost-effective in chemotherapy

Objective

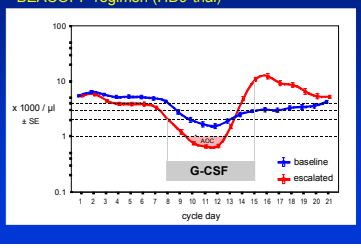
To give an example, how a computer simulation model of human granulopoiesis can be used to suggest optimal cost-effective timing schedules of G-CSF treatment in moderate dose-intensified chemotherapy regimen.

Examples are shown for two different regimen:

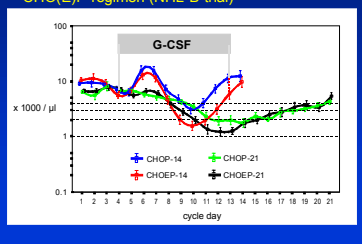
- BEACOPP-regimen
- CHOP-14-regimen

Clinical data

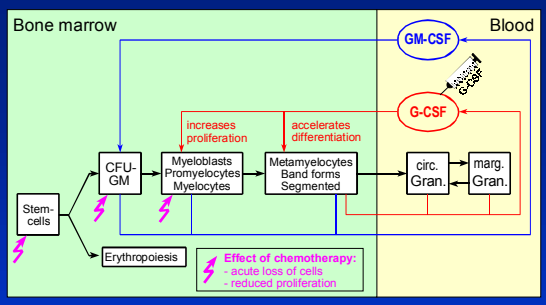
BEACOPP-regimen (HD9-trial)



CHO(E)P-regimen (NHL-B-trial)



Model of human granulopoiesis



Model properties:

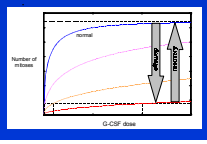
Granulopoietic cell stages are described by compartments, connected by cell fluxes.

Growth factor mediated feedback loops regulate cell production.

Action of G-CSF treatment is described independently from action of chemotherapy.

Assumption:

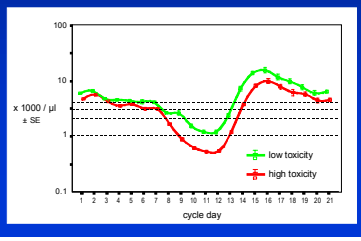
Chemotherapy administration causes a temporary decrease of mitotic responsiveness to the G-CSF stimulus



Method of simulating different timing schedules of G-CSF treatment (Example: BEACOPP-escalated regimen)

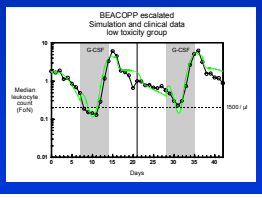
Considering heterogeneity of hematotoxicity

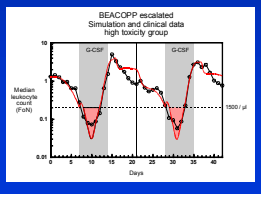
Patients are divided into three toxicity groups. Time course of leukocytes is shown here for the low and high toxicity group.



Simulation for a known G-CSF scheduling

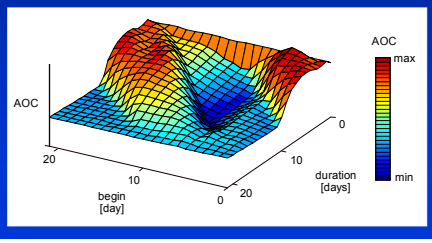
Effect of chemotherapy on acute cell loss and temporary decrease of mitotic responsiveness is adapted for a known G-CSF scheduling, separately for the low and high toxicity group (model fit). The area above the simulated curve and a clinically relevant leukocyte threshold (1500 /µl) is calculated (AOC).





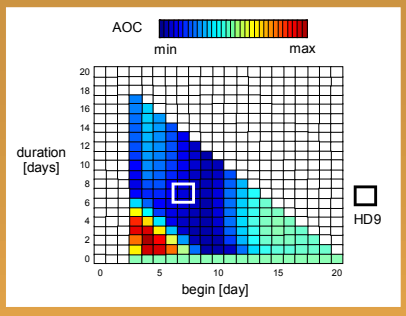
Prediction for unknown timing schedules of G-CSF

Unknown G-CSF timing schedules are simulated by systematical variations of the day of beginning and the days of duration of G-CSF treatment. AOCs are calculated for each schedule and plotted as a surface diagram (here: high toxicity group). Cost-effective schedules are defined to produce minimum AOC at shortest possible duration.

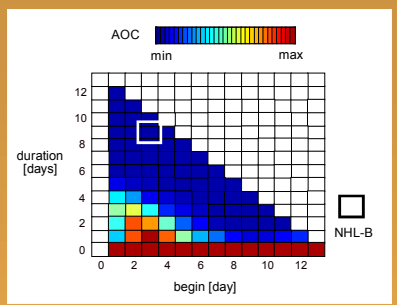


Results for the BEACOPP-escalated and CHOP-14 regimen

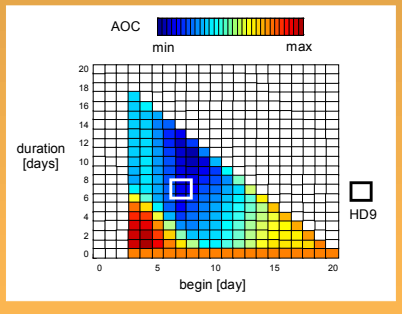
BEACOPP-escalated (low toxicity group)



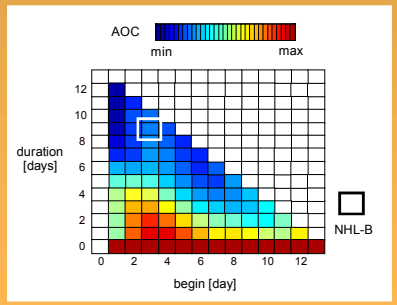
CHOP-14 (low toxicity group)



BEACOPP-escalated (high toxicity group)



CHOP-14 (high toxicity group)



- White squares indicate the fixed G-CSF scheduling given in the regimens
- Deep blue squares indicate low AOC and effective reduction of neutropenia
- The model suggests for both chemotherapy regimen, that G-CSF duration can be reduced in the low toxicity groups, but might needs to be increased in the high toxicity groups

Conclusions, perspectives and open questions

- This mathematical model of granulopoiesis can be used to simulate the time course of leukocytes during chemotherapy treatment +/- G-CSF support.
- It can be used as a tool to identify optimal timing schedules of G-CSF support to reduce costs of intensified chemotherapy regimen with growth factor support.
- Similar models of thrombopoiesis or erythropoiesis may be used to identify optimal timing schedules of other growth factors (TPO, EPO).
- A model based rationale for further clinical trials on growth factor supported chemotherapy regimen can be given.
- The model may be also used to simulate the effect of different dosings of different cytostatic drugs on hematopoiesis

Further clinical data is needed to improve modelling of human hematopoiesis (granulopoiesis, erythropoiesis, thrombopoiesis):

- Data on chemotherapies with different doses of same drugs
- Data on chemotherapies with additions / deletions of one drug
- Data on same chemotherapies +/- G-CSF or varying timing schedules

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