Model-based design of chemotherapeutic regimens that account for heterogeneity in leucopoenia

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Summary

Patients treated with multicycle chemotherapy can exhibit large interindividual heterogeneity of haematotoxicity. We describe how a biomathematical model of human granulopoiesis can be used to design risk-adapted dose-dense chemotherapies, leading to more similar leucopoenias in the population. Calculations were performed on a large data set for cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP)-like chemotherapies for aggressive non-Hodgkin lymphoma. Age, gender, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase and the degree of leucopoenia within the first therapy cycle were used to stratify patients into groups with different expected severity of leucopoenia. We estimated risk-specific bone marrow toxicities depending on the drug doses administered. These toxicities were used to derive risk-adapted therapy schedules. We determined different doses of cyclophosphamide and additional etoposide for patients treated with CHOP-14. Alternatively, the model predicted that further reductions of cycle duration were feasible in groups with low toxicity. We also used the model to identify appropriate granulocyte colony-stimulating factor (G-CSF) schedules. In conclusion, we present a method to estimate the potential of risk-specific dose adaptation of different cytotoxic drugs in order to design chemotherapy protocols that result in decreased diversity of leucopoenia between patients, to develop dose-escalation strategies in cases of low leucopoenic reaction and to determine optimal G-CSF support.

Keywords: mathematical modelling, leucopoenia, chemotherapy, clinical trials.

In recent years, the development of dose-intensified and time-intensified chemotherapeutic regimens for malignant lymphoma and breast cancer has led to improved therapeutic outcomes (Hortobagyi, 2001; Blayney *et al*, 2003; Diehl *et al*, 2003; Pfreundschuh *et al*, 2004a,b; Shipp *et al*, 1995; von Minckwitz *et al*, 2005). However, the granulopoietic toxicity of cytotoxic drugs and the associated risk of neutropenic infections are particularly important limiting factors for treatment intensification, even if granulocyte colony-stimulating factor (G-CSF) is used to ameliorate neutropenia (Bodey *et al*, 1966; Pettengell *et al*, 1992; Trillet-Lenoir *et al*, 1995; Wunderlich *et al*, 2003). Furthermore, the severity of toxicity

is heterogenous between patients even when putatively equal total doses are applied (Gurney, 1996, 2002; Engel *et al*, 2000; Tesch *et al*, 1998; Kloess *et al*, 2001; Wunderlich *et al*, 2003).

For example, elderly patients with aggressive lymphoma have an unfavourable prognosis (The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993; Pfreundschuh *et al*, 2004a,b). Additionally, because of higher myelotoxic reactions, dose escalations cannot be maintained throughout the entire age group (Dixon *et al*, 1986; Wunderlich *et al*, 2003).

There is some evidence that low leucopoenia of patients is associated with a poorer outcome [Hodgkin disease (Broste-

anu *et al*, 2004), breast cancer (Carpenter *et al*, 1982; Poikonen *et al*, 1999), osteosarcoma (Cortes *et al*, 1974), germ cell tumour (Horwich *et al*, 1997), ovarian cancer (Rankin *et al*, 1992)]. It is generally assumed that this is caused by differences in cytotoxic drug metabolism (Sulkes & Collins, 1987; Iyer & Ratain, 1998). Patients with a lower degree of leucopoenia are considered to metabolise drugs faster, resulting in worse tumour control (Gurney, 2002). In this context, the calculation of the drug dose via the body surface of patients is questionable and seems not to be adequate (Gurney, 1996, 2002). Hence, there are attempts to individually adapt dosing of chemotherapeutic drugs during therapy in relation to the degree of leucopoenia (Bergh *et al*, 1998, 2000; Wilson *et al*, 2002). In some circumstances, this approach has been shown to neutralise prognostic factors for therapy outcome (Wilson *et al*, 2002). Hence, it would be interesting to adapt drug dosing and timing to prognostic risk factors for leucopoenia. Such prognostic factors can indeed be identified; however, they do not directly enable the calculation of specific dosing and timing schedules.

We approached this problem by using a biomathematical model of human granulopoiesis under conditions of chemotherapy with G-CSF support that was recently developed by our group (Engel *et al*, 2004; Scholz *et al*, 2004). This model provides an innovative method for estimating the damage of bone marrow cell stages as a function of the applied drug dose on the basis of measured peripheral leucocyte dynamics. The present report demonstrates how this method can be used to adapt the dosing and timing of chemotherapy as a function of expected leucopoenic risk. Knowing that dose escalations cannot be performed for the entire population, it was our objective to estimate the potential of therapy intensification for those patients for whom a low degree of leucopoenia is predicted.

We applied our method in a paradigmatic way to cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP)-like schemes widely used for non-Hodgkin lymphoma (NHL); however, we believe that it could also be used more generally.

Patients and methods

Clinical data

We evaluated peripheral white blood cell counts under chemotherapy collected from patients of the NHL-B trial [German High Grade Non-Hodgkin Lymphoma Study Group (DSHNHL), chairman M. Pfreundschuh, responsible biostatistican M. Loeffler; (Pfreundschuh *et al*, 2004a,b)]. We included patients with confirmed diagnosis. In this trial, four chemotherapies for aggressive NHL with different drug application, cycle duration and G-CSF application were compared (Table I).

Using multivariate regression models, an analysis of the World Health Organization (WHO) grades of leucopoenia of patients, as measured on cycle days in which the nadir phase of leucocyte counts usually falls [days 8–10 for CHO(E)P (CHOP ± etoposide)-14, days 10–12 for CHO(E)P-21], has been performed recently (Kloess *et al*, 2001). It showed that age (>60 years), gender (female), ECOG performance status (>1) [Eastern Cooperative Oncology Group performance status – measures daily living activity of patients (Oken *et al*, 1982)] and lactate dehydrogenase (LDH) serum concentration (>upper normal value; 240 U/l) are risk factors for leucopoenia. Because the odds ratios of these risk factors are comparable, the number of present factors suffices to characterise the individual risk of a patient to experience leucopoenia.

Table II gives an overview of the data. The odds ratios are also provided (Kloess *et al*, 2001). The last column of Table II denotes the allocation of the elderly patients to three risk groups of roughly equivalent size [low risk (LR) with no additional risk factor except for age, medium risk (MR) with one factor, high risk (HR) with two or three factors]. Because the degree of leucopoenia is correlated with the degree of infections (see Fig 1), this classification coincides with different risks groups for infection.

There are only a few or no measurements for the risk groups of young patients with increased LDH, because this was an exclusion criterion for the study. Consequently, the corresponding risk groups could not be analysed.

Although not planned in the trial protocol, some patients treated with CHO(E)P-21 received G-CSF in a few cycles. These cycles were excluded from the analysis because of the occasional very high leucocyte counts, which are untypical for therapies without G-CSF support. Furthermore, measurements on days of therapy delay were excluded. Other discrepancies from the trial protocol, such as deviations from the days 4 to 13 G-CSF scheduling or deviations from the planned drug doses were also excluded, as protocol adherence was excellent, except for the high-risk patients under CHOEP regimens (Pfreundschuh *et al*, 2004a,b).

Table I. Treatment regimens compared within NHL-B trial.

Regimen	G-CSF (d)	Cyclophosphamide (mg/m^2)	Doxorubicin (mg/m^2)	Vincristine (mg)	Etoposide (mg/m^2)	Prednisone (d)	Cycles (*n*, d)
CHOP-21	–	750, day 1	50, day 1	2, day 1	–	1–5	6, 21
CHOP-14	4–13	750, day 1	50, day 1	2, day 1	–	1–5	6, 14
CHOEP-21	–	750, day 1	50, day 1	2, day 1	100, days 1–3	1–5	6, 21
CHOEP-14	4–13	750, day 1	50, day 1	2, day 1	100, days 1–3	1–5	6, 14

G-CSF, granulocyte colony-stimulating factor; NHL, non-Hodgkin lymphoma.

Table II. Leucopoenia risk groups in NHL-B trial; risk factors, number of patients and available measurements per therapy are provided.

Number	Age >60 years	Female	ECOG PS > 1	LDH > unv	CHOP-14, n (meas.)	CHOEP-14, n (meas.)	CHOP-21, n (meas.)	CHOEP-21, n (meas.)	Total	Odds ratio	Number of risk factors	Group
1	y	y	y	y	16 (328)	18 (313)	15 (197)	16 (128)	65 (966)	26·4	4	HR
2	y	y	y	n	6 (94)	9 (160)	6 (102)	0 (0)	21 (356)	8·8	3	HR
3	y	y	n	y	36 (478)	33 (656)	29 (476)	30 (389)	128 (1999)	12	3	HR
4	y	n	y	y	8 (141)	7 (115)	16 (203)	6 (88)	37 (547)	13·2	3	HR
5	n	y	y	y	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	13·2	3	–
6	y	y	n	n	41 (567)	37 (638)	48 (520)	35 (503)	161 (2228)	4	2	MR
7	y	n	y	n	9 (181)	12 (141)	3 (35)	6 (46)	30 (403)	4·4	2	MR
8	y	n	n	y	26 (405)	34 (541)	28 (342)	33 (409)	121 (1697)	6	2	MR
9	n	y	y	n	4 (43)	4 (45)	2 (14)	4 (56)	14 (158)	4·4	2	–
10	n	y	n	y	0 (0)	1 (22)	1 (0)	0 (0)	2 (22)	6	2	–
11	n	n	y	y	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6·6	2	–
12	y	n	n	n	48 (665)	48 (752)	49 (739)	58 (785)	203 (2941)	2	1	LR
13	n	y	n	n	77 (1086)	86 (1315)	68 (921)	65 (869)	296 (4191)	2	1	–
14	n	n	y	n	4 (72)	8 (135)	9 (138)	11 (169)	32 (514)	2·2	1	–
15	n	n	n	y	4 (66)	1 (11)	0 (0)	0 (0)	5 (77)	3	1	–
16	n	n	n	n	114 (1526)	100 (1590)	121 (1463)	123 (1654)	458 (6233)	1	0	–

ECOG PS, Eastern Cooperative Oncology Group Performance Score; LDH > unv, lactate dehydrogenase > upper normal value; HR, high risk; MR, medium risk; LR, low risk; n, number of patients; meas., number of available measurements; NHL, non-Hodgkin lymphoma.
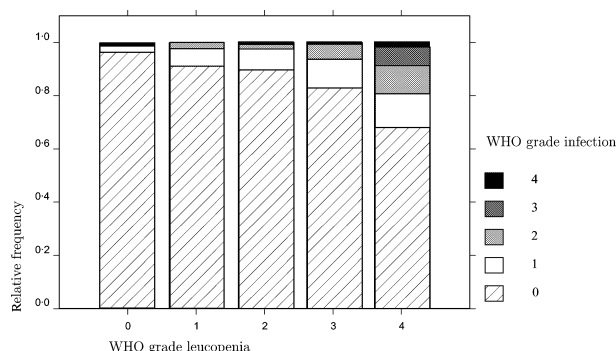

Fig 1. Correlation between leucopoenia and infection [non-Hodgkin lymphoma NHL-B trial].

Model

A short description of our model is presented (see Fig 2). A detailed discussion can be found elsewhere (Engel *et al*, 2004; Scholz *et al*, 2004). The model was based on concatenated cell compartments from early cell stages in bone marrow to mature granulocytes in blood. The system is regulated by growth factor-mediated feedback loops. A simple pharmacokinetic model was added to describe the application of G-CSF.

Major assumptions on the effects of chemotherapy were:

1 Applications of cytotoxic drugs induce an instantaneous depletion in each affected bone marrow cell stage. For reasons of normalisation and in order to make toxicities comparable, this effect was timed to 1 d according to the fast metabolism of the substances (Bender *et al*, 1977; Sinkule, 1984; Busse *et al*, 1997). No persistent damage was assumed (Lohrmann & Schreml, 1982).

2 The cell damage has first-order kinetics (Lohrmann & Schreml, 1982). We defined the ratio of the cell loss rate to the compartment size as (constant) drug-specific toxicity parameter k.

3 Cytotoxic drugs damage independently of each other, i.e. toxicity parameters for drugs in combination were added.

4 We assumed a higher chemosensitivity during the first cycle with increased values of the toxicity parameters (estimated to be +30%). This took into account increased metabolism and lower availability of cytotoxic drugs in subsequent cycles of a multicycle therapy or a reduction in tumor-related cytokine production (Gorschluter *et al*, 1995; Blumenthal *et al*, 2002; Liang *et al*, 2003).

These assumptions proved to adequately explain large clinical data sets of therapies for Hodgkin disease or aggressive NHL (10 different chemotherapies with up to five different cytotoxic drugs) and were discussed in our previous work (Engel *et al*, 2004; Scholz *et al*, 2004).

It was not necessary to assume four different toxicity parameters (k_S, k_{CG}, k_{PGB}, k_{MGB}) for each drug or drug combination because, when modelling the CHOP-like therapies, we could only distinguish between toxicity related to the totality of the drug combination of cyclophosphamide, doxorubicin and vincristine (CHO), which are always applied simultaneously, and the single drug etoposide (E). Therefore, whilst retaining sufficient accuracy, it was possible to set $k_{S-CHO} = k_{CG-CHO}$, $k_{MGB-CHO} = k_{S-E} = k_{CG-E} = 0$ and $k_{PGB-E} = 0\cdot2$ to be constant for all risk groups. The latter two settings implied that etoposide has no stem cell toxicity but has considerable effects on proliferating precursor cells. In addition, for high leucopoenic risk groups, the parameter $k_{PGB-CHO}$ could
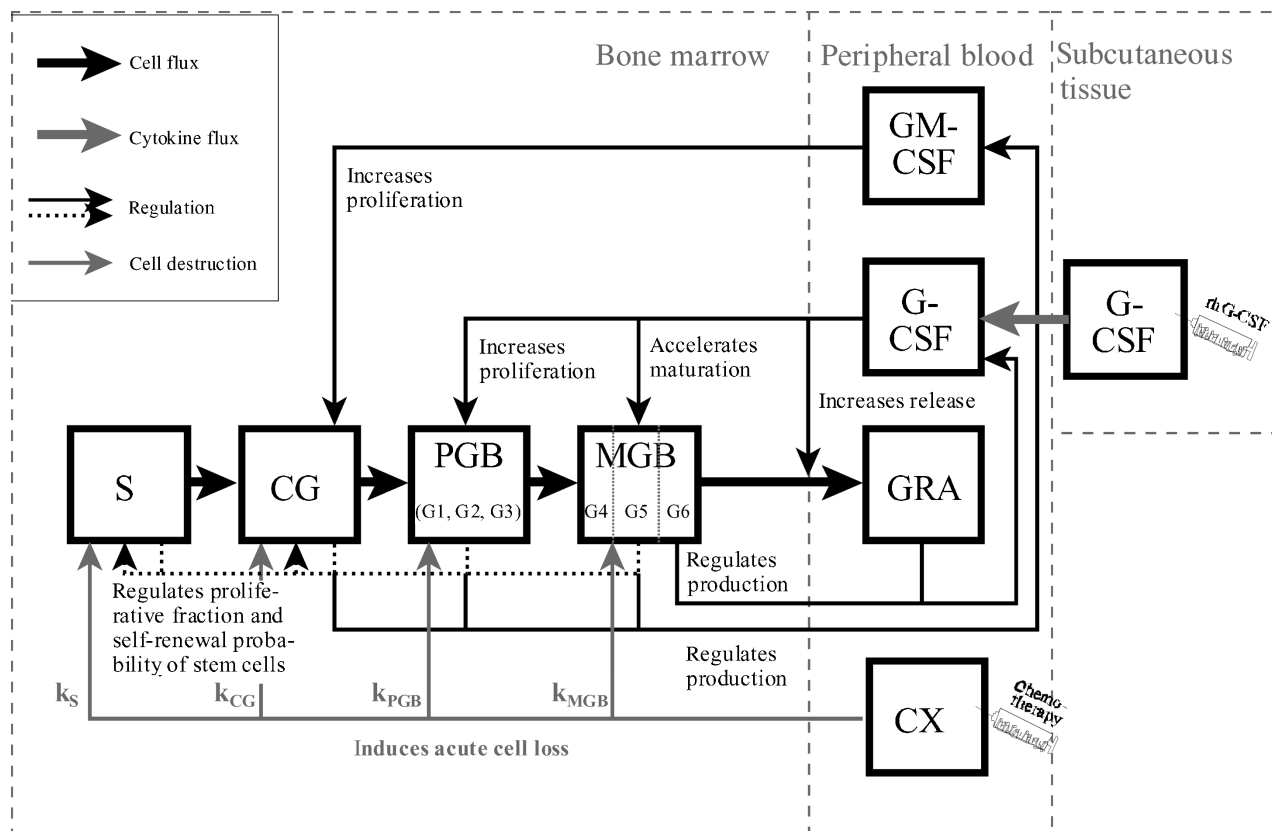
Fig 2. Schematic model structure (S, haematopoetic stem cells; CG, granulopoetic progenitors; PGB, granulopoetic precursors; MGB, maturing pool; GRA, granulocytes; G(M)-CSF, granulocyte (macrophage) colony-stimulating factor; CX, chemotherapy).

only be estimated up to a lower bound because of an almost complete exhaustion of the corresponding cell compartment.

Consequently, we used only two free parameters to model the CHOP therapies (k_{S-CHO}, $k_{PGB-CHO}$) and only one additional free parameter for CHOEP therapies (k_{MGB-E}).

Modelling leucopoenic heterogeneity and data-fitting procedure

To account for the risk groups in our model, we made the following additional model assumption:

5   Risk factors are associated with differences in bone marrow toxicity parameters, rather than differences in model parameters affecting pharmacodynamics.

Hence, we modelled the effect of the leucopoenia risk groups only with different toxicity parameters. For this, higher risk groups were associated with greater toxicity parameters resulting in higher estimated bone marrow toxicity. Parameters related to granulopoietic dynamics were kept constant for all risk groups.

The three free toxicity parameters could be estimated by fitting the model to clinical data. As granulocyte counts are not available from the clinical trials, we used leucocyte counts to fit our model of granulopoiesis. This was justified by a strong correlation between leucocytes and granulocytes, both for large

and very small cell numbers (Li *et al*, 1984; Benson *et al*, 1985; Brigden *et al*, 1991) which can also be confirmed by our own data (see *Supplementary Material*, Fig S1). We searched for the parameter set with best-fit between model and data. Optimally, the differences between the logarithms of model prediction and data would be as small as possible. We used logarithms to ensure a particularly good fit of the nadir phase. The optimisation problem was solved numerically using evolutionary strategies. Details of these non-deterministic optimisation algorithms can be found elsewhere (Rechenberg, 1984, 1994; Schwefel, 1984).

Each risk group was fully characterised by a specific set of the three free toxicity parameters valid for all four regimens considered.

Dose-toxicity functions

In the present study, dose-toxicity functions described the dependence of toxicity parameters on drug doses. In our previous analysis, we determined dose-toxicity functions for etoposide and the combination of cyclophosphamide and doxorubicin in young patients (Scholz *et al*, 2004). The data for this analysis were taken from a phase II trial for dose-escalated CHOEP regimen. Doxorubicin was increased only to a small extent because of its dose-limiting cardiovascular

toxicity. For this reason, we did not investigate dose escalations for this drug in the present analysis. However, we used the dose-toxicity function for the combination of cyclophosphamide and doxorubicin as an upper limit for dose-escalated cyclophosphamide. Hence, all predictions for dose-escalated cyclophosphamide were conservative.

We made the following further model assumption:

6 Risk-specific dose-toxicity functions are obtained by scaling established dose-toxicity functions for young patients. This was performed on the basis of the different toxicity parameters determined for different risk groups under the dosage of conventional CHO(E)P regimens (e.g. see Fig 3). Each of these toxicity parameters defined one point of the risk-specific dose-toxicity functions.

Because of flat dose-toxicity functions, the parameters $k_{\text{PGB-CHO}}$ and $k_{\text{PGB-E}}$ were considered to be dose-independent for all risk groups.

Model simulations and comparison between model and data

Model curves for regimens and risk groups considered were determined by initialising our model of granulopoiesis with the risk-specific toxicity parameters according to the schedule of the drugs. Furthermore, the planned schedule of G-CSF application was imprinted into the model. The model simulation provides relative changes of cell counts, which were
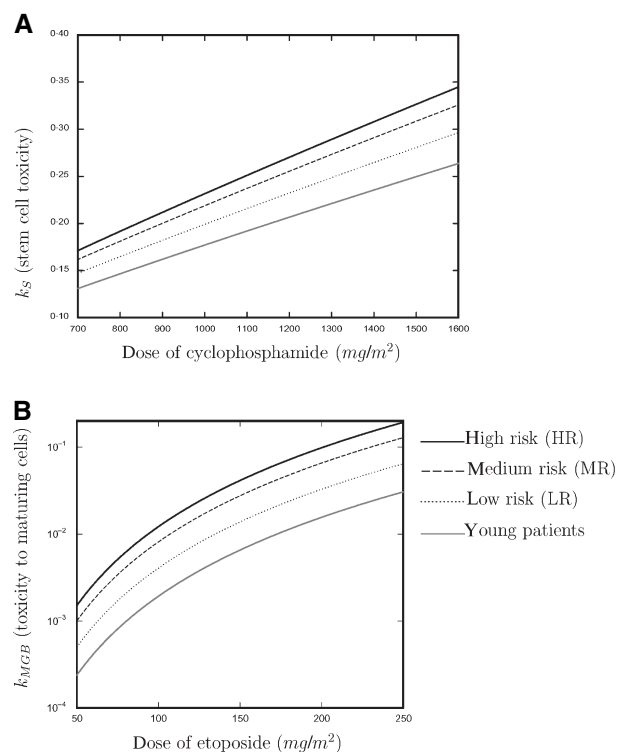
Fig 3. Scaled dose-toxicity functions for young patients and the risk groups for elderly patients.

normalised to a baseline of 7×10^9 leucocytes/l in order to compare model and data as described above.

Tolerability criteria for simulated regimens

To ensure the clinical feasibility of our model-designed regimens, we specified four criteria that should be fulfilled either alone or in combination. Therefore, we defined (i) a critical value for area over the curve (AOC; which is the area between the model curve and the line of 4×10^9 leucocytes/l), (ii) duration of leucopoenia (DoL; the total time with leucocytes $<4 \times 10^9$/l measured over six cycles), (iii) minimal recovery value [MRV; which is the minimal leucocyte count (MLC) at the end of any cycle] and (iv) MLC during therapy respectively. A regimen is assumed to be feasible, if the corresponding population medians are better than the critical values. We examined whether model predictions for various intensified regimens and risk groups comply with these criteria. Furthermore, the above quantities were compared with model predictions for regimens and risk groups for which clinical experience was available.

Results

Adaptations of chemotherapy regimens based on pretherapeutic risk factors for leucopoenia

At first, model fitting yielded distinct toxicity parameters for each of the risk groups listed in Table II except for those excluded for lack of measurements (three risk groups of young patients with high LDH). According to the predictions from the statistical model, we found a good linear relationship between the number of risk factors and the toxicity parameters (e.g. $k_{\text{S-CHO}}$, see Fig 4).

In the next step, we restricted our considerations to elderly patients. They were pooled into three leucopoenia risk groups (Table II). Again, model fitting yielded distinct toxicity parameters for each of the groups (Table III). With these parameters, we obtained a good agreement between the median of the leucocyte data and the model prediction. Figure 5 presents the results for CHOP-14. The data of the other therapy regimens fit equally well (results see *Supplementary Material*, Fig S2).

Using these parameters, we estimated dose-toxicity functions for the three risk groups of elderly patients in comparison with the younger age group (Fig 3).

We then predicted leucopoenia for novel scenarios of risk-adapted therapies. For the subsequent examples, we used the conventional CHOP-14 regimen with G-CSF on days 4–13 over six cycles as baseline therapy. At first, we compared the model curves for this therapy with respect to the risk groups (Fig 6B).

Scenario 1. We considered cyclophosphamide dose escalation. Figure 7 shows the predicted toxicities based on model simulations using the dose-toxicity functions. If one
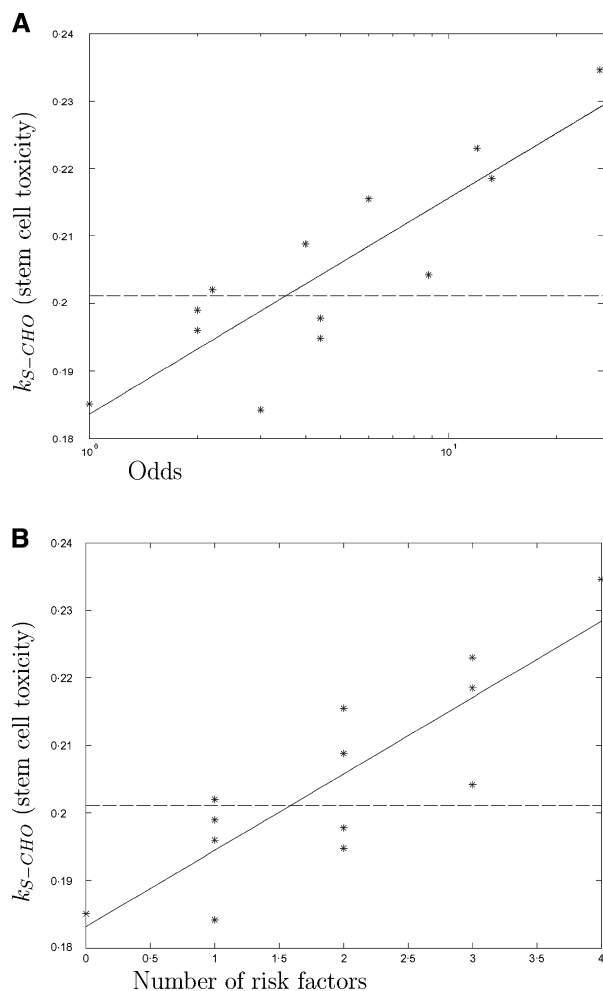
Fig 4. Correlation between odds ratio, number of risk factors and toxicity parameters. The dotted line indicates the parameter for the pooled population that is without any distinction of risk groups.

Table III. Results of model fitting: estimates of the model toxicity parameters.

Parameter	LR	MR	HR
$k_{S\text{-CHO}}$	0·19	0·21	0·22
$k_{PGB\text{-CHO}}$	0·06	0·10	0·2 (>0·1)
$k_{MGB\text{-E}}$	0·004	0·008	0·012

HR, high risk; MR, medium risk; LR, low risk.

stipulates that, e.g. the DoL for the LR-group and MR-group should be similar to the DoL of the HR-group under conventional CHOP-14, we estimate that the cyclophosphamide dose for the LR-group can be increased by 280 (mg/m^2) and for the MR-group by 100 (mg/m^2). Such a differential dosing according to risk groups resulted in a similar toxicity profile in each group (Fig 6C).

Other requirements can be analysed analogously. Corresponding critical values for the leucopoenic characteristics should be compared with model predictions for clinically

approved regimens. A corresponding reference table summarising the observed toxicity profiles in the different risk groups is provided (Table IV). When making comparisons, we took into consideration that the CHOEP-14 regimen was too toxic for the HR-group and therefore, several dose reductions were performed. The same was true for the CHOEP-21 regimen for the same group, where additional G-CSF was often used to ensure punctual treatment continuation.

Scenario 2. We analysed the application of additional etoposide to the CHOP-14 regimen. If etoposide is given to the LR-group as in the CHOEP-14 regimen (100 mg/m^2, days 1–3) and also to the MR-group with half of the dose, we predict comparable toxicities for all risk groups (Fig 6D; the HR-group receives conventional CHOP-14).

Scenario 3. Finally, we investigated the possibility for further cycle time reductions of the CHOP-14 regimen (Table V). Our model simulations showed that within the LR-group the CHOP chemotherapy can be performed with a cycle duration of 11 d without being more toxic than CHOP-14 in the HR-group (i.e. AOC, DoL, MLC and MRV are better or equal). The cycle duration for the MR-group can also be shortened by 2 d. Further shortening of cycle duration would be more toxic than CHOP-14 for the HR-group, independently of the G-CSF scheduling. Under the precondition that G-CSF application should be stopped 2 d before the start of the next cycle, the G-CSF schedules of the intensified regimen described in Table V were estimated to be optimal. For MR, there were two G-CSF schedules (days 5–11 and days 6–11), which were considered to be equal. The G-CSF-scheduling days 6–11 was predicted to be better in AOC and MLC but worse in DoL and MRV than the scheduling days 5–11.

Risk adaptations of chemotherapy based on toxic reaction during the first treatment cycle

In a separate approach, we determined the toxic reaction of all patients (young and old) during the first cycle of therapy and subsequently divided the population into two subpopulations according to the median of the MLCs [LRFC (low risk in first cycle, i.e. MLC at first treatment cycle was greater than median) and HRFC (high risk in first cycle, i.e. MLC was less than median), see Table VI)]. Again, for these risk groups the toxicity model parameters could be estimated (Table VII, Fig 8).

We propose a CHOP-14 with G-CSF days 4–13 regimen adapted for the degree of leucopoenia of the patients at the first cycle of therapy. In the first cycle, all patients receive the same dose. Allocation to the risk groups was determined by the leucocyte counts collected at this cycle. The HRFC-group continues to receive the standard dose level. For the LRFC-group, we predict that the cyclophosphamide dose could be increased by 360 mg/m^2 for cycles 2–6 without being more toxic than the HRFC-group with the standard dosage (see Table VIII).
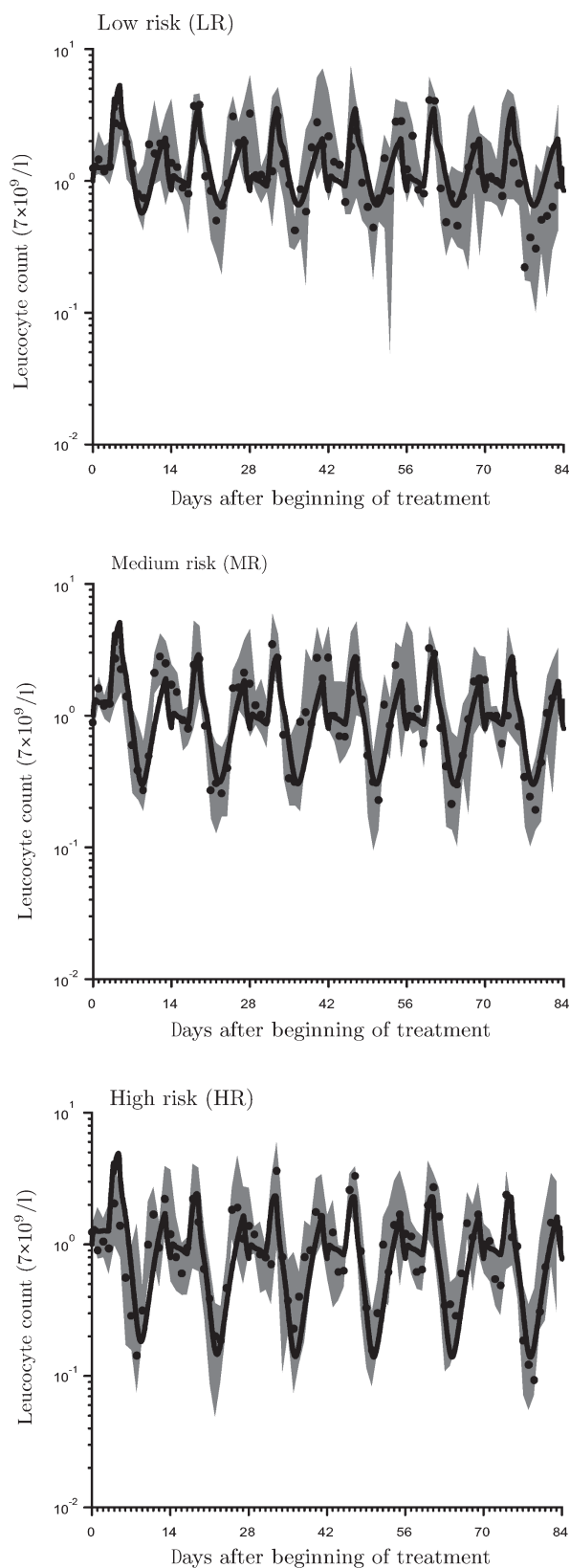
Fig 5. Example of model and data comparison for CHOP-14. Points are median leucocyte counts and the grey area is the interquartile range, continuous curves are model predictions (CHOP-21, CHOEP-14, CHOEP-21, see Fig S2).

Discussion

Routine dosing of chemotherapy is commonly based on body surface calculations, irrespective of the observed heterogeneity of side-effects. As the knowledge of prognostic factors for adverse events grows, the new challenge is to provide a rational basis for quantitative modifications of therapy schedules.

We present an innovative method to individualise chemotherapy dosing and timing in a model assisted way, that aims to decrease the diversity of leucopoenia when compared with those observed under standard regimens. In addition to a pure phenomenological statistical approach (Kloess *et al*, 2001), we modelled the physiological responses of granulopoiesis during chemotherapy with G-CSF support. This model has been validated on the basis of large clinical data sets recently (Engel *et al*, 2004; Scholz *et al*, 2004). In the present study, we explored possible applications within the framework of planning of clinical trials. Recently, several promising approaches to address clinical problems with biomathematical granulopoiesis models have been reported (Colijn & Mackey, 2005a,b; Friberg *et al*, 2002; Engel *et al*, 2004; Ostby *et al*, 2004; Scholz *et al*, 2004; Sandstrom *et al*, 2005; Vainstein *et al*, 2005).

In our model, different leucotoxic drug reactions can be characterised by parameters that describe the cell loss rate of bone marrow cell stages with respect to the drugs used. In our analysis we assumed that risk factors for leucopoenia are associated with differences in these toxicity model parameters. This assumption was supported by observed heterogeneities in drug metabolism (Sulkes & Collins, 1987; Iyer & Ratain, 1998) and the relationship between drug availability *in vivo* and (myelo)toxicity reported by several authors [e.g. doxorubicin (Rushing *et al*, 1994), etoposide (Bennett *et al*, 1987)]. Furthermore, it was shown that the effect of G-CSF differs little between young and old patients (Chatta *et al*, 1994).

Risk-specific toxicity parameters were estimated by fitting our model to the data using a recently established method (Engel *et al*, 2004; Scholz *et al*, 2004). Toxicity parameters were determined with respect to a (risk) group of patients and over multiple cycles. Therefore, they must be interpreted as the mean toxicity in the corresponding group of patients. Nevertheless, a first cycle correction was made. The number of free parameters was kept as small as possible, making the model simple and preventing over-fitting of data. We used only three free parameters to characterise the toxicity for a given risk group under CHO(E)P regimens (two for the toxicity related to cyclophosphamide + doxorubicin + vincristine and one for the toxicity related to etoposide).

To demonstrate the potential of our modelling method, we evaluated the data of the NHL-B trial for aggressive NHL. Four pretherapeutical risk factors for leucopoenia are known (Kloess *et al*, 2001). On the basis of these factors, we analysed the full pretherapeutical risk model of 16 risk groups. We found a good linear correlation between the number of risk factors and toxicity parameters. This confirmed the suitability of our risk model
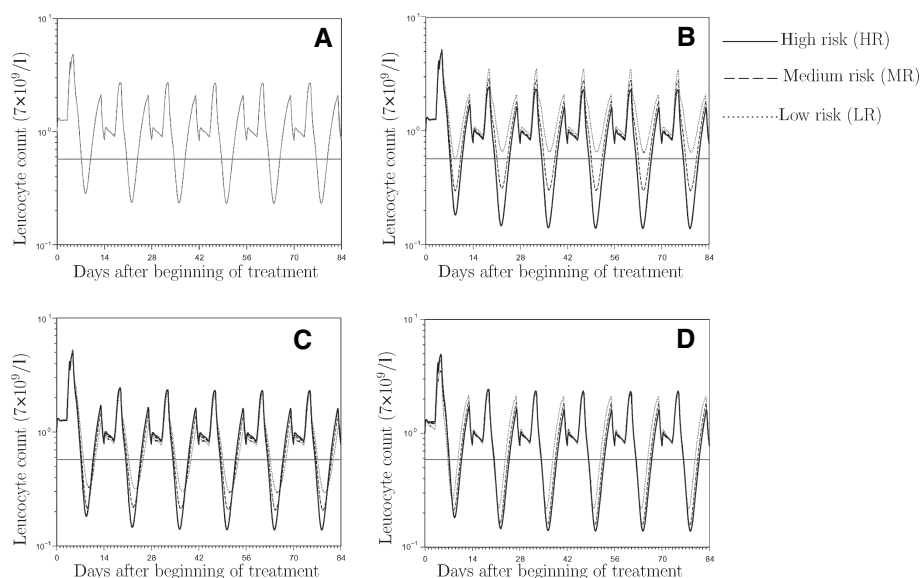
Fig 6. Median model predictions for the risk groups of elderly patients. The horizontal line represents a leucocyte count of 4×10^9/l. (A) conventional CHOP-14 without distinction of risk groups; (B) conventional CHOP-14 with distinction of risk groups; (C) risk adapted cyclophosphamide dosage; (D) risk adapted additional etoposide application.
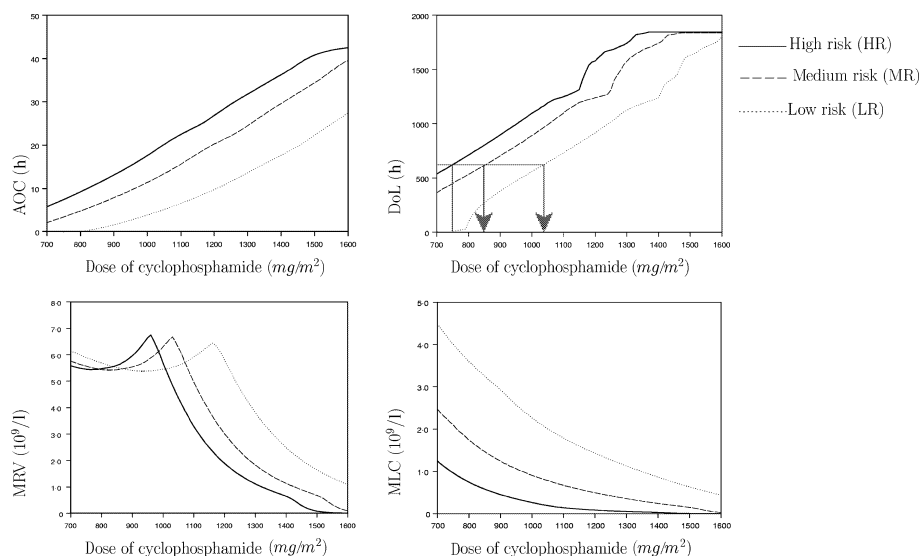

Fig 7. Model-based toxicity predictions for CHOP-14 regimen with increasing doses of cyclophosphamide. The four panels describe the toxicity criteria, the three curves describe the three leucopoenia risk groups for elderly patients.

based on the pure number of the statistically identified risk factors also from our model point of view, which, in contrast to the statistical approach, is fitted not only to the nadir phase of leucocytes but also to the complete leucocyte dynamics.

The quantitative differences in toxicity between the pretherapeutical risk groups allow the analysis of risk-adapted therapies. The starting point for our calculations was the CHOP-14 regimen with conventional G-CSF on days 4–13 for elderly patients. Administration of peg-G-CSF has not been considered so far. We showed examples of different adaptation

strategies based on dose escalation or decreasing cycle duration of the therapy for certain risk groups. These proposals are now integrated into the planning for forthcoming DSHNHL trials. An upcoming trial should compare standard CHOP-14 with individualised CHOP-14 with respect to feasibility, toxicity and outcome.

We have previously shown in the past that predictions based on our model can be validated by clinical trials (Engel *et al*, 2004; Scholz *et al*, 2004). Based on this model, the CHOP-14 in the RICOVER trial was performed with G-CSF administered

Table IV. Toxicity criteria for established regimen (median model prediction).

Regimen	Risk group	AOC (d)	Duration of leucopoenia (h)	Minimal recovery value (10^9/l)	Minimal leucocyte count (10^9/l)
CHOP-14	LR	0·0	0	5·9	4·0
CHOP-14	HR	7·4	620	5·5	1·0
CHOEP-14	LR	4·6	480	5·9	1·5
CHOEP-14	HR	8·2	650	5·5	0·8
CHOP-21	LR	10·2	1700	4·4	2·0
CHOP-21	HR	19·6	2100	4·1	0·7
CHOEP-21	LR	18·3	2000	4·3	0·7
CHOEP-21	HR	20·5	2100	4·1	0·6

AOC, area over the curve; HR, high risk; LR, low risk.

Table VII. Toxicity parameter settings for the intratherapeutic risk groups.

Parameter	LRFC	HRFC
$k_{\text{S-CHO}}$	0·18	0·21
$k_{\text{PGB-CHO}}$	0·05	0·10 (>0·1)
$k_{\text{MGB-CHO}}$	0·002	0·006

LRFC, low risk in first cycle, i.e. minimal leucocyte count at first treatment cycle was greater than median; HRFC, high risk in first cycle, i.e. minimal leucocyte count at first treatment cycle was lower than median.

only on days 6–12, which resulted in acceptable toxicity as predicted by our model [leucocyte data and corresponding model curves are shown in Ref. Engel *et al* (2004) and Scholz *et al* (2004); toxicity analysis is currently an unpublished observation]. However, further validation of our model is necessary; e.g. on the basis of data of other patient collectives or data of studies for which we made toxicity estimates.

To predict whether a therapy is feasible or not, we calculated four criteria obtained from our model simulations AOC, DoL, MLC and MRV. The second and third criterions are known to be related to infections (Bodey *et al*, 1966). The first is a combined measure of the second and third. The fourth criterion is often used in clinical practise to decide on treatment continuation in time. From a clinical point of view, it is not clear which of these criteria is the most useful for therapy feasibility decisions. Therefore, and because of the fact that all model predictions are only estimates for the median of the corresponding group, we compared our proposals for risk-

adapted therapies with predictions for clinically approved regimens with respect to the said criteria.

The proposed increments of cyclophosphamide and etoposide dose in certain risk-adapted therapies (scenarios 1 and 2) were based on dose-toxicity functions obtained from a phase II trial for young patients. For cyclophosphamide dose escalation, the used function made conservative predictions. We scaled the dose-toxicity functions to the toxicity baselines of our risk groups obtained for the dosages in NHL-B. Consequently, toxicity in high-risk groups is always higher than for low-risk groups and was expected to increase more rapidly at higher doses.

In comparison, analysis of further decreasing cycle duration (scenario 3) did not require dose-toxicity functions. We also estimated optimal G-CSF schedules for corresponding therapies.

Finally, we analysed the effects of an intratherapeutical risk-based adaptation of the therapy for the entire population. We found that the degree of leucopoenia during the first cycle is a good predictor for leucopoenia in subsequent cycles and estimated an exceptional dose escalation feasible for one half of the population. However, our decision to assign patients to the

Table V. Risk-specific reduction of cycle duration for CHOP-14.

Regimen	Risk group	AOC (d)	Duration of leucopoenia (h)	Minimal recovery value (10^9/l)	Minimal leucocyte count (10^9/l)
CHOP-14 (G-CSF days 4–13)	HR	7·4	620	5·5	1·0
CHOP-11 (G-CSF days 5–10)	LR	1·9	360	5·4	2·6
CHOP-12 (G-CSF days 5–11)	MR	5·3	580	6·7	1·5
CHOP-12 (G-CSF days 6–11)	MR	4·6	660	6·6	1·8

AOC, area over the curve; G-CSF, granulocyte colony-stimulating factor; HR, high risk; MR, medium risk; LR, low risk.

Table VI. Allocation numbers of the intratherapeutic risk groups; in comparison with Table II, patients without any measurements at the first cycle or with G-CSF at the first cycle under CHO(E)P-21 regimen were excluded from our analysis.

Risk group	CHOP-14, *n* (meas.)	CHOEP-14, *n* (meas.)	CHOP-21, *n* (meas.)	CHOEP-21, *n* (meas.)
Low risk	181 (2412)	188 (2718)	163 (1936)	147 (1811)
High risk	182 (3113)	190 (3597)	179 (2941)	161 (2914)

G-CSF, granulocyte colony-stimulating factor; *n*, number of patients; meas., number of available measurements.

Table VIII. Risk during therapy adapted dosing of cyclophosphamide.

Cyclophosphamide dose (mg/m²)	Risk group	AOC (d)	Duration of leucopoenia (h)	Minimal recovery value (10⁶/l)	Minimal leucocyte count (10⁶/l)
750	High risk	3·8	475	5500	2000
1110	Low risk	2·3	473	5400	2700

AOC, area over the curve.

A

CHOP-14, low first cycle risk
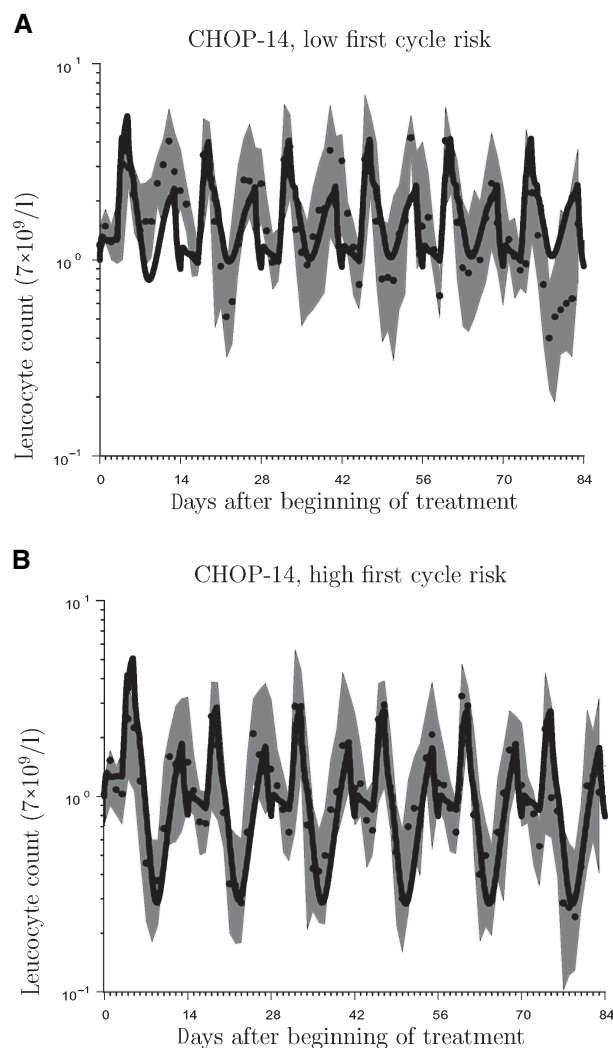
B

CHOP-14, high first cycle risk

Fig 8. Intratherapeutic risk groups, model and data comparison.

risk groups as a function of the lowest available leucocyte count at the first cycle is an approximation and could be improved within a possible future clinical trial by mandatory blood collections in the nadir phase.

There are many more possibilities for risk-adapted therapy designs than described above. One could vary, for example, the baseline therapy (CHOP-14). One could also analyse additional drugs or other drug dose escalations. Finally, it would be possible to redefine the risk groups, e.g. on the basis of other or additional factors, such as those for which a direct metabolic influence is known (liver and kidney functions, genetic factors) or by combining pretherapeutic and intratherapeutic factors. The latter issue and the integration of G-CSF administration, which is important for any dose-escalated regimen, is an advantage of our model in comparison with recently proposed semi-physiological models for therapeutic drug monitoring (Friberg *et al*, 2002; Sandstrom *et al*, 2005).

Because dose-reduction strategies are very common in trial protocols, in our analysis we only considered therapy intensifications in cases of low toxic response. Nevertheless, our method could also be used to provide estimates for reduction of leucopoenia when drug doses are reduced. This could be interesting in the context of B-cell NHL, for which the role of chemotherapy in combination with the novel antibody rituximab is under discussion. In this case, we can analogously determine risk-specific dose reductions to harmonise toxicity and/or to prevent high-grade leucotoxicity. However, this approach implies that non-inferiority trials would be required.

The present report evaluated only data collected from aggressive NHL therapies. However, it would be possible to apply our analysis to other diseases and chemotherapies for which there is a rationale of dose escalation limited by leucopoenia (e.g. breast cancer). For good quality results, it is necessary to have a sufficiently large database of leucocyte counts on different days of chemotherapy cycles and good protocol adherence with respect to dosage and scheduling of drugs and G-CSF. In this case, our model could be used for feasibility analysis in the planning phase of further clinical trials based on the drugs considered and could be a complementary addition to dose-effect models already at hand (Hasenclever *et al*, 1996, 2001).

Our method could be a further approach to harmonise the leucopoenic reaction of patients (Kobayashi & Ratain, 1993). Although we did not obtain total individualisation of therapy, a convergence on the basis of easily determined factors was found. We did not abandon the dosing schedule based on body surface area, because all available data were obtained on the basis of that system. However, we suggested adaptations to reduce known weaknesses of possible improper dosing and to increase therapy efficacy.

Our method could include both, pretherapeutical and intratherapeutical factors to adapt dosing, as claimed in literature (Gurney, 1996). Consequently, our model could help to reinforce toxicity harmonisation strategies already performed in certain clinical trials (Wilson *et al*, 2002).

Acknowledgements

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Supplementary Material

The following supplementary material is available for this article online:

Fig S1. Relationship between leucocytes and granulocytes. 262 observations from five patients receiving myelosuppressive chemotherapy for Hodgkin or non-Hodgkin lymphoma ($R^2 = 86\%$ after logarithmic transformation).

Fig S2. Comparison of model and data. All risk groups of elderly patients and all therapies of NHL-B trial. Red dots are median leucocyte counts of patients; blue curves are inter-quartile ranges; black curves are model predictions.

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