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Dirk Hasenclever · Oana Brosteanu · Torsten Gerike
Markus Loeffler

Modelling of chemotherapy: The effective dose approach

Abstract We sketch the development of the effective dose approach which provides a theoretical framework to interpret chemotherapy outcome data. Building on the generalised Skipper model of chemotherapy, a meta-regression method is derived to jointly analyse all chemotherapy comparing randomised clinical trials in a given malignancy in order to explore the slope of the effective dose/outcome relationship and the relative potency of cytostatic drugs. The model is applied to explain why treatment differences in aggressive NHL appear to differ by risk groups in aggressive NHL. A respective meta-subgroup analysis to confirm this interaction hypothesis is proposed.

Introduction

Theoretical modelling of chemotherapy is hampered by the discouraging plethora of factors that might – potentially – influence the outcome, but on which there is negligible specific knowledge. This is the basic reason for the widespread scepticism towards theorising in chemotherapy design. We maintain that nevertheless valuable theoretical insights may be obtained. The purpose of this article is to sketch the development and results of our approach so far. At the end, we present a model based hypothesis explaining why treatment differences in aggressive NHL appear to differ by risk groups.

We start out with an admittedly oversimplified model chosen to capture just the major and well acknowledged determinants of chemotherapy outcome. The model is mathematically developed to quantitatively predict the outcome of certain clinical trials. It is thus confronted retrospectively with the body of evidence available in the literature and prospectively with results of trials the design of which the model has been used to define and optimise.

D. Hasenclever (✉)
University of Leipzig, IMISE, Liebigstr. 27,
D-04103 Leipzig, Germany
e-mail: Hasenclever@IMISE.uni-Leipzig.de
Tel.: 0341-9716121

The model is refined stepwise in an prediction/observation loop, i.e. only if data force us to complicate it (Ockham's razor principle). The leading idea of this top down modelling strategy is that one has to get first order effects right before one can meaningfully tackle those of second or higher order.

Step 0: The Skipper model

The Skipper textbook model of chemotherapy was established in the 1960s. We take it as a starting point: Equal doses of chemotherapy cause equal proportional reductions of the tumour cell load. Chemotherapy shots are additive on the logarithmic scale. During treatment intervals the tumour re-grows exponentially, that is linearly on a log scale.

From this simple model it is clear that a) the total amount of chemotherapy determines the gross log cell kill and b) the total treatment duration determines the regrowth during treatment pauses. The outcome i.e. the net log tumour cell kill is approximately determined by the difference: gross log cell kill – log regrowth. We call this important relation the treatment balance equation.

The Skipper model is supported by data from animal models. These animal models obviously are quite artificial as compared to a clinical trial population: In a clinical trial patients' tumours differ considerably a) in size and chemosensitivity and b) in their growth kinetics. In an experimental setting this heterogeneity may be controlled for -in a clinical context these two types of heterogeneity must be accounted for:

Refinement step 1: Account for patients' heterogeneity: The generalised Skipper model

The generalised Skipper model (GSM) essentially is the mathematical combination of the idea of the Skipper model (mainly the treatment balance equation) and a representation of the heterogeneity in chemosensitivity and growth kinetics observed in clinical trials. Each pa-

tient's tumour is assumed to have its specific chemosensitivity and its characteristic latency time (i.e. time from few cells to clinically detectable tumour). In order to represent heterogeneity of a patients' population, chemosensitivity and latency times are assumed to follow a latent stochastic distribution within the study.

We assume a convenient parametric form for this distribution (in accordance with Ockham's principle until better knowledge is available). Latency times follow a log-normal distribution, while the characteristic chemosensitivity independently follows an extreme-value distribution. (Model implications derived are always checked not to depend on the particular choice of the parametric form of this distribution). The GSM thus becomes a parametrical statistical model that can be fitted to time to progression curves from clinical trials. Mathematical details of the GSM will be published elsewhere (manuscript in preparation).

We used this model to explore the effect of dose reductions and treatment delays in the treatments actually given. In Hasenclever 1996 [4], we published the prediction of the existence of a clinically exploitable total dose/outcome relationship in Hodgkin's disease based on fitting the model to individual clinical data on outcome and treatment given. This prediction was prospectively confirmed in the large BEACOPP trial of the German Hodgkin's disease study group [1], in the design of which we were involved.

The main achievement of this first refinement step is that the model was connected to clinical data from study populations. It thus became empirical and passed a first test of its predictions.

One weakness of the GSM lay in the implementation of the concept of "total amount of chemotherapy" or total dose. We simply used relative total dose measured by the percentage of the dose given with respect to the planned dose in a standard regimen averaged over all cytostatic drugs employed. Beside ignoring possible second order effects (schedule effects, drug interactions etc.), this assumes that all cytostatic drugs employed are equipotent at standard doses.

This approach is legitimate by Ockham's principle in the absence of further specific knowledge and had already been used by Hryniuk and DeVita. Nevertheless it is desirable to estimate equipotency relations between different cytostatic drugs. To estimate equipotency relations, information from as many relevant clinical trials as possible is required. This highlighted another weakness: The application of the model was limited to analyse individual patients' data. It was not yet able to connect to evidence from randomised trials published in the literature.

Refinement step 2: Make use of published evidence and estimate equipotency relations: Metaregression analysis of all randomised chemotherapy comparing trials

What information on treatment effects and on chemotherapy can be extracted from a publication of a randomised chemotherapy comparing trial?

a) A measure of the difference between the progression free survival curves. Assuming a proportional hazard model (as is done in COX regression) a statistically natural measure is the log hazard ratio (lhr) (i.e. the coefficient of the treatment effect in the COX model). The lhr estimate can be approximately read off the curve plots. The standard error of the lhr estimate can be obtained from the total number of events which usually should be contained in the paper.
b) The planned total doses for all drugs used and the total planned treatment duration for all regimens compared.

To make use of this type of data, we define a measure of chemotherapy strength, the effective dose, containing unknown parameters namely equipotency weights for the cytostatic drugs. We then link the observed treatment difference quantified as log hazard ratio with the planned difference in treatment strength by a suitable regression equation from which the unknown parameters may be estimated with standard statistical methods.

Such a meta-regression equation is easily derived by Taylor expansion: In any two arm randomised chemotherapy trial:

$$\mathrm{lhr}(\text{arm1 vs. arm2}) \doteq g \times (\mathrm{strength}(\text{arm1}) - \mathrm{strength}(\text{arm2})) + \text{terms of third order}$$

i.e.: the log hasard ratio as measure of the outcome difference is approximately linearly related to the difference in chemotherapy strength of the trial arms compared. The proportionality constant g measures the slope of the effective dose/outcome relationship.

All we need to use this equation is an adequate summary measure of treatment strength. First of all, we define the summary total dose as the weighted sum of the total doses of the individual drugs employed. The weights are unknown parameters to be estimated. They serve to project different drug doses on a common total dose scale on which they add up. Secondly, according to the Skipper model we have to somehow adjust for differences in treatment duration.

The well known Hryniuk concept of summary dose intensity [5] just divides summary total dose by treatment duration. This concept was developed to predict response rates in a setting when cycling treatment was given until maximal response. It follows mathematically from the GSM that the response rates in this special setting indeed essentially depend on the dose intensity (multiplied by a tumour entity specific constant).

However, if the task is to model long term outcome and cure rates of chemotherapies which stop after a fixed number of cycles the concept of dose intensity has two conceptual shortcomings:

a) The dose intensity of one cycle is the same as that of say 8 cycles. Dose intensity does not take total dose into the account.
b) The correction for tumour regrowth with dose intensity is independent of the characteristic average growth kinetics of the tumour entity in question. The correction

is the same whether or not the malignancy is slowly or rapidly growing. Dose intensity does not take the disease specific growth kinetic into the account.

Derived from the GSM we instead define the effective dose:

effective dose:
=total dose/(1+treatment duration/average latency time)

The denominator is a correction for treatment length that eliminates the two flaws. Note that this formula is intuitive: duration/latency time is a proxy for the fraction of the tumour that re-grows during treatment intervals. For cure, the treatment has thus not only to eradicate one tumour, but (1+treatment duration/average latency time) tumour.

The average latency time is a characteristic of the tumour entity or the study population. It can be estimated from the meta-regression or be read off the form of the time to progression curves by directly fitting the GSM. We thus gain in biologic specificity.
The GSM further implies:

a) Logarithm of the effective dose is the measure of chemotherapy strength to be used in the meta-regression equation and
b) The log effective dose should be approximately linearly related to the cure rate i.e. the plateau of time to progression curves.
c) The proportionality constant g in the meta-regression equation is inversely related to the amount of heterogeneity of the cellular chemosensitivity in the study population: The smaller the heterogeneity in the study population, the steeper the chemotherapy strength/ outcome relationship. Note that this is intuitive: If a fraction of patients is cured in a rather homogeneous patient population, then those not yet cured cannot be far from cure and thus might profit from moderate treatment intensification.

A meta-regression analysis of all available randomised trials in a certain tumour entity becomes feasible, if one can assume that the average latency time L and the heterogeneity in chemosensitivity do not vary too much across study populations (joint g and L across trials!).

Does the model stand the empirical test? In Hodgkin's disease (HD) an analysis of 68 evaluable published pair-wise comparisons shows that the GSM captures major determinants of treatment outcome. As predicted, there is a clear linear relationship between the observed lhr and the difference in log effective dose calculated from the planned treatments in the trial arms (Fig. 1), showing a clinically relevant log effective dose/cure relationship. Log effective doses correlate linearly with three year progression free survival rates (rho=0.79) as expected. Rough estimates for equipotency relations are obtained which are in line with clinical intuition and single agent phase II data. Doxorubicin is confirmed as most important drug in HD. The average latency time is estimated to be about 490 days. Details of this analysis will be published elsewhere (Hasenclever in preparation).

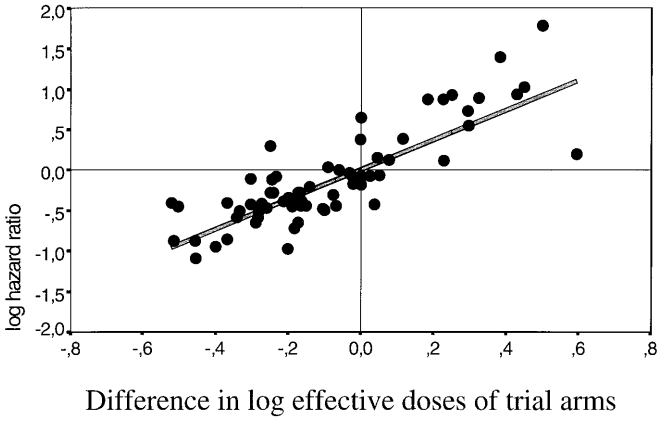

Fig. 1 Meta-regression in Hodgkin' disease (see text)

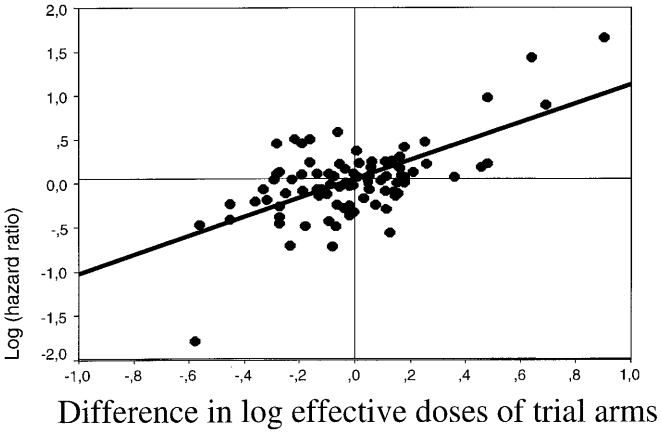

Fig. 2 Meta-regression in NHL (see text)

We conclude that the approach leads to meaningful results at least in a homogeneous situation as in HD.

In aggressive Non Hodgkin lymphoma (aNHL) an analogous analysis of 78 evaluable published pair-wise comparisons (including relevant proportions of diffuse large cell cases) shows a less convincing picture. There is only a trend of a linear relationship between the observed lhr and the difference in log effective dose of the trial arms, which is less pronounces than in HD (Fig.2).

Nevertheless estimates for equipotency relations are obtained which are in line with clinical intuition and single agent phase II data and confirm that doxorubicin, cyclophospamide and etoposide are among the most potent cytostatic drugs in aggressive NHL. The average latency time is estimated to be about 132 days, markedly shorter as in HD as fits clinical impression. Details of this analysis will be published elsewhere (Hasenclever in preparation).

Why is the NHL analysis less satisfactory than the HD one? Does this disprove the GSM or does this provide a clue for model refinement? Results in NHL trials have been sobering in the last 20 years. Thus it is not surprising that the effective dose/outcome relation is less pronounced. It is clear that in NHL the heterogeneity of patients within study populations is much larger than in HD and this - according to the model - implies a less

steep effective dose/outcome relation. Thus the less steep effective dose/outcome relation is not unexpected.

On the other hand, the model fit is far from perfect, indicating that there may be some relevant aspect that is not yet taken into the account.

Refinement step 3: Deal with heterogeneity across study populations

The meta-regression assumes that

a) there is a joint average latency time L constant across study populations
b) there is a joint slope constant g for all trials, i.e. that the heterogeneity in chemosensitivity within the study population is roughly the same across trials. This assumption is much better met in HD (mostly advanced stage) trials than in NHL where inclusion vary much more – criteria in particular as concerns histology.

Both assumptions may be violated in NHL, while being approximately fulfilled in HD.

Subgroup- and cross-trial heterogeneity in average latency time

Item a) is the most critical: Standard 8 CHOP-21 chemotherapy takes 168 days which is larger than the estimated latency time of 132 days in NHL. Thus the effective dose formula implies that differences in treatment duration should matter in NHL as the regrowth during treatment may be substantial (greater 1 tumour!). In contrast in HD, e.g. 8 ABVD treatment takes 224 days which is about half the estimated latency time of 490 days. This implies that differences in treatment duration play a minor in HD.

In addition, if the average latency time is in the order of the treatment duration and there is indication of large heterogeneity as concerns growth kinetics as in NHL, then there must exist a subgroup of patients of considerably faster growth. Looking at the formula for the effective dose, this implies that treatment duration becomes a truly dominating factor in this segment of patients with the most rapidly growing lymphomas. On the other hand, in the complement, a slower growing subgroup, treatment length is expected to be a factor of second order only.
Thus the effective dose concept predicts

a) that reducing treatment intervals should be clinically relevant in aggressive NHL
b) that this effect should mainly be relevant in the subgroup of patients with the most rapidly growing lymphomas.

Can one define this subgroup? Analysing the form of time to progression curves (Fig. 3) by LDH level confirms the clinical impression that high LDH is associated with aggressive growth characteristics. The latency time may be roughly read off the curve as the median time to relapse in responding patients that eventually relapse. High LDH is strongly correlated with IPI high and intermediate high risk groups. Thus trials in low risk only or high risk only differ markedly in average latency time L.

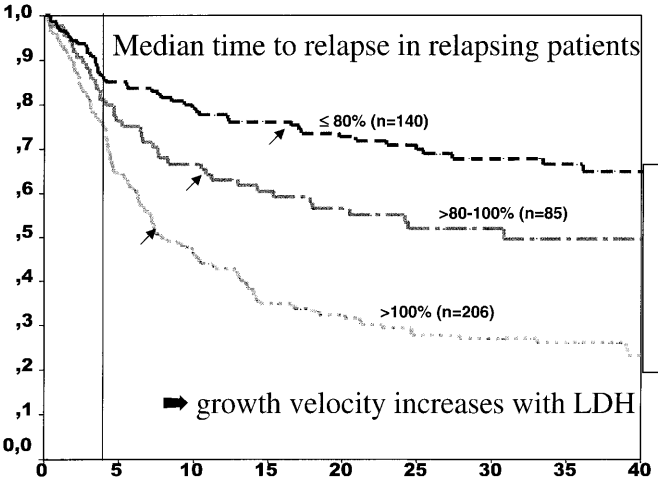

Fig. 3 Time to progression by LDH level from the NHL-B trial

Thus the effective dose model predicts that treatments of different intensity and length may differ differently within low and high LDH (respective low and high risk) subgroups. The shorter, more intense treatment should have a differential benefit in the aggressively growing subgroup. This is an interaction hypothesis that can be empirically tested.

The most informative trial for this prediction is the four arm NHL-B trial of the German aggressive NHL study group that compared CHOP variants given in 14 or 21 day intervals. The shortening was accomplished with G-CSF support. The trial closed in June 2000. Preliminary results were orally presented in Saarbruecken. Data of the first 228 patients over 60 years of age treated with CHOP show Symposium (Pfreundschuh 2000 personal communication) that

a) the reduction of treatment intervals of CHOP from 3 to 2 weeks (with G-CSF support) was possible in nearly all cases
b) reduction of treatment intervals improved CR rates, progression free survival and overall survival.
c) This treatment length effect is mainly concentrated in the high LDH subgroup.

CR rates	All	LDH ≤ N	LDH > N
CHOP-21	56.8 %	74.6%	39.0%
CHOP-14	74.3 %	80.4%	67.3%

The NHL-B trial thus preliminarily supports

a) the model's prediction of the importance of treatment intervals in NHL and
b) the interaction hypothesis, that high intensity matters most in the presence of aggressive growth.

The final analysis is due in 2002.

Subgroup and cross-trial heterogeneity in the slope of the effective dose outcome relationship, i.e. in chemosensitivity heterogeneity of the study populations

The GSM provides a formula relating the slope of the log effective dose outcome relationship to the freedom from progression rate at end of treatment, the freedom from progression plateau and a factor correcting for latency time. (Unfortunately as the tails of the chemosensitivity distribution is involved, this formula is numerically to instable to be used in data extraction, i.e. to read off the slope from published curves.)
Nevertheless the model qualitatively implies:

a) The slope g becomes steeper with shorter latency times (not only the calculated effective dose).
b) The slope g becomes steeper with a higher proportion of patients that respond but eventually relapse.

Note that both implications are plausible: a) Rapid growth may give rise to purely kinetic resistance i.e. the tumour responds well to chemotherapy but treatment fails due to massive regrowth during treatment intervals in the presence of a generally high cellular chemosensitivity. b) The patients that respond but eventually relapse form the sub-population of those that are not too far from cure and might thus profit from moderate increases in effective dose.
When we compare low risk and high risk subgroups in NHL both items apply: High risk patient population have a shorter latency time (eg. 66 days vs. 264) and a higher proportion of responding but relapsing patients (e.g. 35% vs. 25%). The model predicts that the slope of the log effective dose outcome relationship should be steeper in high risk than low risk. According to a conservative estimate the slope in high risk should be at least 1.4 the slope in low risk. This effect is independent from the modification of the log effective dose differences due to the use of different average latency times.

This slope effect thus combines with and strengthens the differential effects due to differing regrowth kinetics in low and high risk subgroups. As a result, the model predicts clinically relevant subgroup effects, namely that the benefit from intensified and/or dose escalated treatment should be more pronounced in the high risk subgroup. This may be important in trial design. It provides a rationale for running trials separately within low and high risk groups as several study groups recently decided to do.

Is there evidence for such a pattern? Several randomised trials in intermediate and aggressive NHL report that treatment differences differed between low and high risk groups, although most trials are underpowered to show statistical significance of a subgroup effect.

Linch [7] reported a differential benefit from PACE-BOM over CHOP in stage IV. Haioun [3] reports that there is a benefit from high dose chemotherapy consolidation with stem cell support after 4 ACVBP, but only confined to IPI high and high intermediate risk patients. Recently Tilly [10] described that the difference between 3–4 ACVBP+GELA-consolidation and 8 m-BACOD increases monotonously and significantly with each additional IPI risk factor from zero to substantial. (For other reports see [6, 8, 11]).

All these reports of subgroup effects appear to be in reasonable quantitative agreement with model predictions calculated using the equipotency weights from the aNHL meta-regression and assuming subgroup specific latency times and slopes as described above. The model thus provides a joined explanation to several reports of a differential treatment effects most pronounced a high risk subgroup.
To be fair, we have to admit that in some of the paper the information on the subgroup effect is sparse and two other trials [2, 9] in which the model would expect trends for a larger effect in high risk patients do not mention the interaction effect. To avoid publication bias and to corroborate the interaction hypothesis we propose therefor to organise a meta subgroup analysis ideally based on individual data in all trials for which the model predicts a relevant subgroup effect.

Conclusions

We have shown that the effective dose approach provides a theoretical framework to interpret various clinical trial results in a coherent way. This integrated view of all available evidence generates hypotheses to be tested prospectively. Thus a prediction/observation feedback loop is established. The strength of the approach is its refinement strategy: After getting first order effects right, second order effects not yet incorporated come into focus through their contrast against model predictions.

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