

Review

Rationale for dose escalation of first line conventional chemotherapy in advanced Hodgkin's disease

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Summary

Which strategy is more promising to improve the outcome of primary conventional chemotherapy in advanced Hodgkin's disease (HD): a moderate dose escalation or treatment intensification by shortening cycles? The answer generally depends on two factors: the tumour growth velocity and the chemosensitivity of the tumour. A simple mathematical model of tumour growth and chemotherapy effects was developed to quantify this dependency. The model allows to estimate the distribution of latency times (i.e., the time a tumour requires to grow from one cell to clinical detection) and the distribution of chemosensitivity in a patient population on the base of clinical data on tumour control and treatment given. The model was fitted to the data of 705 stage IIIB/IV HD patients of the German Hodgkin's Lymphoma Study Group (GHSG). The model reveals considerable

heterogeneity in chemosensitivity and a significantly positive slope of the dose-response relationship at the standard treatment dose level. The model can be used to simulate the effect of various treatment escalation and intensification strategies. On the basis of such simulations we predict only small benefits (about 3% in 5-year tumour control rates) with shortening cycle intervals from 4 to 3 weeks. In contrast, we predict that a moderate dose escalation by 30% of a standard chemotherapy will lead to a potential benefit in the order of 10% in tumour control at 5 years. The presently ongoing HD9 trial of the GHSG is designed to demonstrate this effect.

Key words: chemotherapy, dose response relationship, Hodgkin's disease, randomized clinical trials, statistical models, tumour growth kinetics

Introduction

About 50% of the patients with advanced stage Hodgkin's disease can be cured with standard chemotherapy. When in 1991 the GHSG started to design the HD9 trial for advanced Hodgkin's disease, it was felt that one should try to improve this rate by treatment intensification made possible by growth factor support. According to the Hryniuk concept of dose intensity, intensification can be achieved either by shortening intervals between cycles or by increasing doses or both. However, there is no concept available to decide which of these strategies is most promising for a specific tumour entity. It is the objective of this paper to provide a model-based approach to this problem.

Basic concepts

To start we remind the reader of the well-known textbook model of chemotherapy [1] (Figure 1). The course of treatment depends on two factors: the tumour regrowth during the treatment intervals and the chemosensitivity of tumour cells at each treatment shot.

The relative impact of interval shortening evidently

increases with tumour growth velocity, i.e., the slope of the tumour regrowth. The impact of additional dose depends on whether the cell kill of each shot is the same (as in Figure 1) or is reduced in later shots due to selection of less chemosensitive tumour cells. The Hryniuk concept of dose intensity, being unspecific to tumour biology, does not allow to take these factors into the account.

For most tumour entities cell counts, doubling times and chemosensitivity are difficult to measure directly in

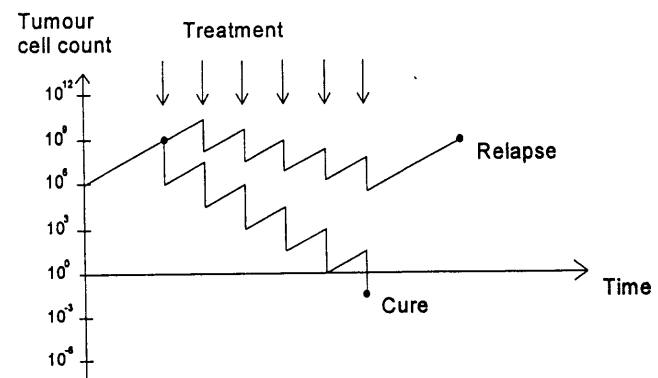


Figure 1. Textbook model of tumour growth and chemotherapy.

individual patients. In addition, these characteristics clearly vary considerably between patients. We will show here that one can nevertheless obtain a meaningful description of tumour growth and chemosensitivity on a population scale if one accepts some simplifying model assumptions. Subsequently, we will show how to estimate the distribution of latency times (i.e., the time a tumour requires to grow from one cell to clinical detection) and the distribution of (relative) chemosensitivity from clinical data.

Model assumptions

(1) *Assumptions on tumour growth* We assume that the tumours grow exponentially in each patient with a fixed growth rate during treatment intervals and after treatment. To model the heterogeneity of tumour growth between patients we assume that the growth rates vary according to a lognormal distribution. This is in line with the results of measurements of tumour doubling times in the literature [2].

(2a) *Assumption on chemotherapy effect.* We assume in a first approximation that the efficacy of a treatment depends on two variables: total dose given and treatment duration. We measure treatment duration as the time from the first to the last shot of a chemotherapy regimen. We quantify total dose relative to the standard treatment as the proportion of standard dose given during the entire treatment averaged over all drugs used.

(2b) *The concept of net treatment efficacy.* In one patient, the overall treatment results in a certain net tumour cell kill at the end of treatment. If the net tumour cell kill is greater than the initial tumour cell burden the patient is cured. Otherwise the remaining tumour cells grow until a relapse is detected. Since the absolute tumour cell counts are difficult to measure, we introduce the ratio:

$$TE = \frac{\log(\text{net tumour cell kill})}{\log(\text{initial tumour cell count})}$$

This ratio measures the treatment efficacy of a treatment in a patient. It has an easy clinical interpretation: If the treatment efficacy is zero, treatment has no effect, if it is less than one the patient is destined to relapse. If the net treatment efficacy is greater than 1, the patient is cured and if it is considerably greater than 1, the patient is overtreated by the given therapy.

(2c) *Potential treatment efficacy.* Given the tumour's growth rate, the treatment duration determines the amount of regrowth during treatment pauses. To achieve a certain net treatment efficacy the dose must be sufficient in order to eliminate the regrowth occurring during treatment intervals. Thus the net treatment

efficacy results as a difference of the potential treatment efficacy of the therapy (i.e., as if there were no regrowth) and the regrowth (measured on a log scale relative to the initial tumour cell burden). This fundamental relationship quantifies the balance between the effect of dose and regrowth.

(2d) *Assumptions on chemosensitivity.* We express the chemosensitivity of a patient's tumour by the potential treatment efficacy of the standard treatment. We model interpatient heterogeneity by assuming that the chemosensitivity varies according to a gamma distribution in the population. This distribution is assumed to be independent of the distribution of the latency times.

(2e) *Total dose and potential treatment efficacy.* In order to take the dose-response-relationships into account, we need to specify the relation between total dose and potential treatment efficacy.

We assume a simple power law (cf. Figure 2), introducing the residual chemosensitivity (RCS) as the slope of this function as the standard dose level. RCS = 1 means a linear relation, while RCS < 1 implies a weaker impact of additional dose as one would expect, e.g., in case of selective survival of less chemosensitive tumour cells.

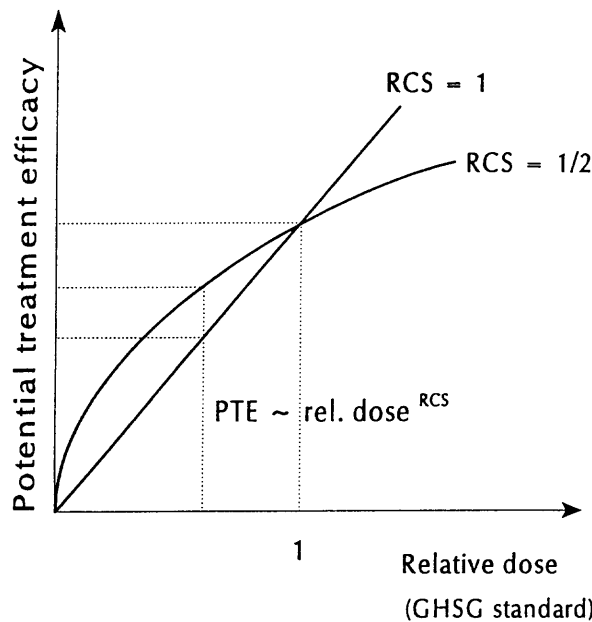


Figure 2. Potential treatment efficacy as a function of total dose. The residual chemosensitivity (RCS) is the slope of the function at standard total dose.

(3) *Model estimation.* The above assumptions define a statistical model of tumour growth and chemotherapy with 5 unknown parameters (two parameters for the lognormal distribution of latency times, two for the gamma distribution of chemosensitivity, and the slope parameter (RCS). These parameters can be estimated from clinical data by maximum likelihood methods. For details see [3].

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Results

The model was fitted to the data of 705 stage IIIB/IV Hodgkin's disease patients treated with COPP/ABVD or COPP/ABV/IMEP polychemotherapy in the trials HD3 and HD6 of the German Hodgkin's Lymphoma Study Group.

There was considerable heterogeneity in treatment given, i.e., relative dose and treatment duration (Table 1). The model fit is good as can be seen from Figure 6. The estimated latency time distribution (Figure 3) is biologically plausible. It has a single mode at one year, the median at 2 years, the mean at 3 years and spreads out to about 10 years.

Figure 4 shows the distribution of the net treatment efficacy (TE) with standard treatment. Negative values of TE clinically correspond to progression during therapy (12%), values between 0 up to 1 responding patients that are destined to relapse (30%), patients with $TE > 1$ are cured (58%). It is remarkable that the mode of Figure 5 is near the cure threshold. This implies that there is a relevant percentage of patients almost cured that might profit from treatment intensification. About 20% of the patients are estimated to have a treatment efficacy beyond 2, which suggests that they might have been cured about with half the chemotherapy (e.g., 4 cycles). These patients appear to be over-treated although unfortunately there is no effective way to preidentify the individual case.

The residual chemosensitivity RCS, i.e., the slope of the potential treatment efficacy as a function of relative total dose at standard therapy dose level, is estimated to be 0.98, i.e., this function appears to be perfectly linear. A lower 95% confidence limit for RCS is 0.5, hence clearly positive. This finding implies that dose escalated shemes should be effective (Figure 5).

Figure 5 illustrates that a moderate dose escalation of standard chemotherapy may be clinically relevant and could have an effect that can be detected by a reasonably sized trial.

Simulation of intensification strategies

Model simulations were used to answer the initial question of the preferable intensification strategy. For this purpose all estimated parameters were kept fixed and only the total dose of the standard chemotherapy resp. the treatment intervals were modified. The model pre-

Table 1. Relative dose and duration of treatment.

	Relative total dose	Treatment duration (months)
Minimum	0.12	0.5
25% quartil	0.85	7.4
Median	0.94	8.3
75% quartil	0.98	9.4
Maximum	1.3	14

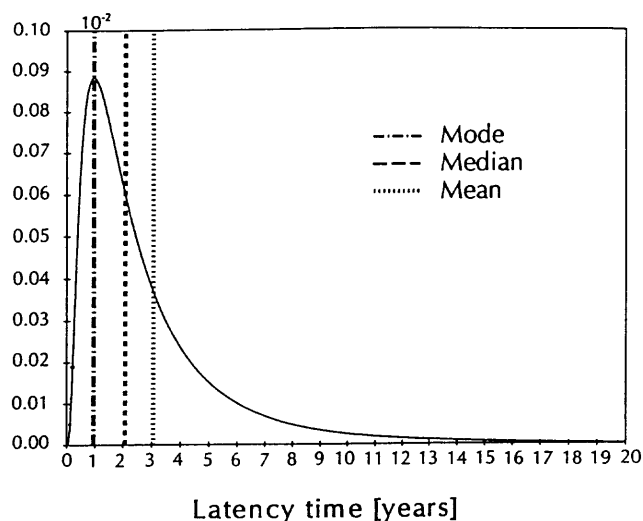


Figure 3. Estimated latency time distribution.

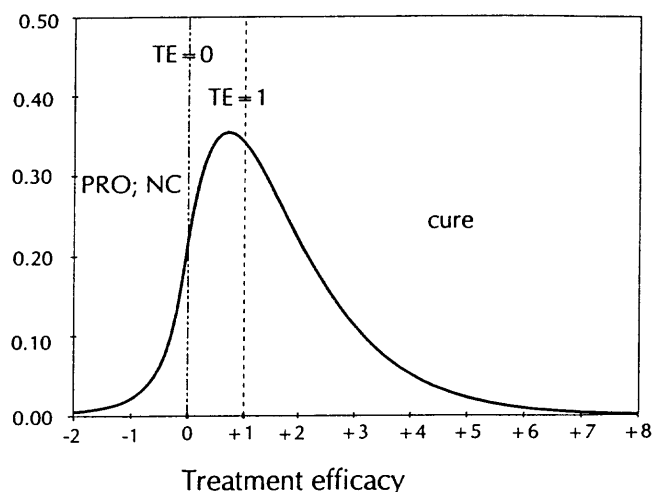


Figure 4. Distribution of the net treatment efficacy with standard treatment.

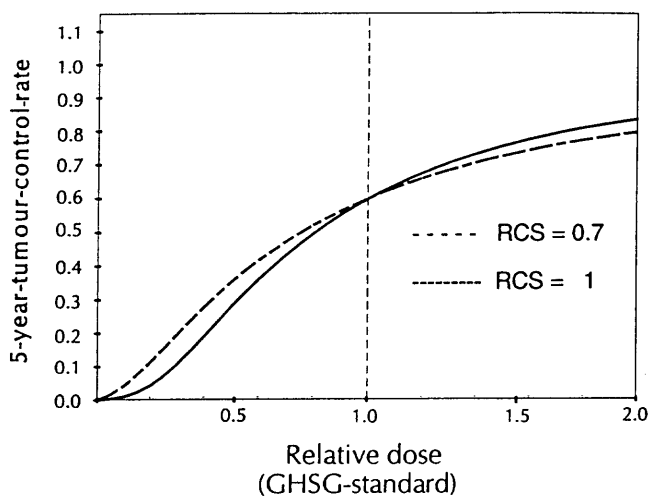


Figure 5. 5-Year tumour control rates with standard treatment as a function of relative total dose.

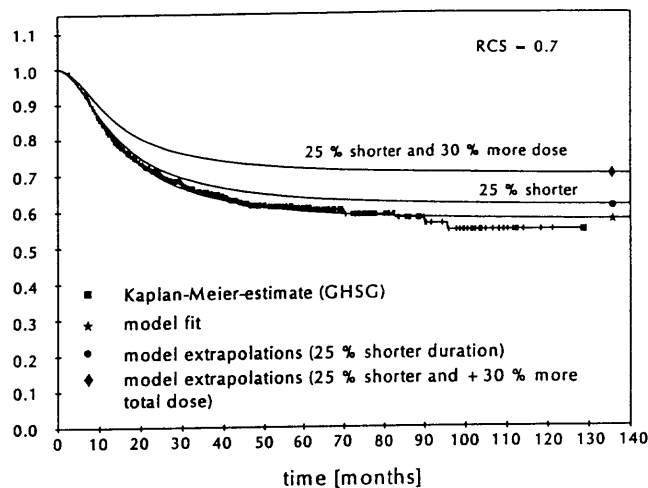


Figure 6. Model fit to the Kaplan-Meier curve and simulated tumour control curves for a) reduction of cycle duration from 4 to 3 weeks; and b) reduction plus 30% increase in total dose.

dicts a potential benefit in the order of only 3% in 5-year tumour control rates if one selectively shortens cycle intervals from 4 to 3 weeks. In contrast, a moderate dose escalation of 30% is predicted to increase long term tumour control rates by more than 10%.

In 1993 the GHSG started the three-armed HD9 trial for advanced stage HD patients comparing standard COPP-ABVD with a 3-weekly standard BEACOPP regimen (essentially the same drugs and dosages rearranged) and a 3-weekly dose escalated BEACOPP [4] with G-CSF support (Table 2). In this escalated BEACOPP scheme cyclophosphamide, adriamycin and etoposide are given in relative dose of 1.9, 1.4 and 2.0, respectively, compared with the standard BEACOPP. This accounts for an average of 30% higher dose intensity. Eight cycles of chemotherapy are given. Figure 6 shows the model based prediction of the trial outcome. This trial will include 1000 patients and should have the statistical power to detect the predicted benefit of about 12%–13% with dose escalated 3-weekly BEACOPP relative to standard COPP-ABVD.

Table 2.

		Standard BEACOPP	Escalated BEACOPP
Cyclophosphamide	i.v. d1	650 mg/m ²	1250 mg/m ²
Adriamycin	i.v. d1	25 mg/m ²	35 mg/m ²
Etoposide	i.v. d1–3	100 mg/m ²	200 mg/m ²
Procarbazine	p.o. d1–7	100 mg/m ²	100 mg/m ²
Prednisone	p.o. d1–14	40 mg/m ²	40 mg/m ²
Vincristine	i.v. d8	2 mg	2 mg
Bleomycin	i.v. d8	10 mg/m ²	10 mg/m ²
G-CSF	s.c. d8+	–	+

Discussion

A model is a simplification of reality. No model substitutes for a well planned clinical trial. The model presented here essentially extends the simple well known textbook model of chemotherapy by incorporating heterogeneity concerning tumour growth and chemosensitivity.

The estimates of the model parameters and thus the predictions rely on the analysis of the treatment given. The potential pitfalls of such retrospective analyses are well known [5]. Our model should be more immune to these pitfalls than usual analyses, because the main confounding factor, i.e. the heterogeneity in chemosensitivity between patients is explicitly incorporated in the model.

The main clinical result of our analysis is that in advanced Hodgkin's disease intensification by dose escalation is predicted to be more effective than intensification by shortening of cycles. That total dose is important has already been described in several retrospective analyses of MOPP therapy (e.g., [6]).

This paper explicates the rationale of the ongoing HD9 trial of the GHSG from a biometrical point of view. The HD9 trial is designed to demonstrate the effect of a moderate (about 30%) dose escalation. HD9 is probably the first randomized trial in the field for which the outcome has been quantitatively predicted. 600 patients are already randomized and the final results will be known in a few years.

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