

Impact of first- and second-line treatment for Hodgkin's lymphoma on the incidence of AML/MDS and NHL—experience of the German Hodgkin's Lymphoma Study Group analyzed by a parametric model of carcinogenesis

M. Scholz^{1,2*}, A. Engert³, J. Franklin³, A. Josting³, V. Diehl³, D. Hasenclever¹ & M. Loeffler¹

¹Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig; ²LIFE (Leipzig Interdisciplinary Research Cluster of Genetic Factors, Phenotypes and Environment), University of Leipzig, Leipzig; ³Klinik 1 für Innere Medizin, University Hospital of Cologne, German Hodgkin Study Group, Cologne, Germany

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Background: Using a parametric carcinogenesis model, we disentangle the superimposing effects of primary and relapse therapies of Hodgkin's disease on secondary neoplasias.

Patients and methods: We analyze eight randomized trials of the German Hodgkin's lymphoma study group [5357 individuals, 67 secondary acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS) and 97 secondary non-Hodgkin's lymphoma (NHL)]. Primary therapies were divided into four groups: radiotherapy alone, moderately dosed COPP/ABVD-like chemotherapies for intermediate and advanced stages and BEACOPP escalated.

Results: For secondary AML/MDS, the hazards after primary therapies are proportional (maximum at 3.4 years), while the hazard after relapse therapy is more peaked (maximum at 1.8 years). Intermediate and advanced stage chemotherapy resulted in a cumulative risk of 1.5%, while the risk after BEACOPP escalated is higher (4.4%, $P = 0.004$) and comparable with that after relapse therapy (4.5%). For secondary NHL, there are no differences in cumulative risk between the primary therapies (2.9%), while the risk after relapse therapy is increased (6.6%, $P = 0.002$).

Conclusions: BEACOPP escalated moderately increases the risk of secondary AML/MDS but not NHL. No differences were found between other chemotherapies of advanced stages and intermediate stages. Secondary AML/MDS occurs faster after relapse treatment than after primary treatment.

Key words: BEACOPP escalated, carcinogenesis model, Hodgkin's lymphoma, secondary AML/MDS, secondary NHL

introduction

The development of dose-dense conventional poly-chemotherapies (CT) for the treatment of Hodgkin's lymphoma significantly improved the therapy outcome [1]. The German Hodgkin Study Group (GHSG) developed the combination therapy with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) escalated regimen (total doses per therapy cycle: bleomycin 80 mg/m², etoposide 600 mg/m², doxorubicin 35 mg/m², cyclophosphamide 1200 mg/m², vincristine 1.4 mg/m², procarbazine 700 mg/m² and prednisone 560 mg/m²) which proved to be superior compared with former standard COPP/ABVD and conventionally dosed BEACOPP [2]. A recently published 10-year follow-up revealed a clear

advantage of BEACOPP escalated with respect to freedom from treatment failure and overall survival [3].

On the other hand, dose-escalated regimens increase the risk of acute and chronic toxicity due to unspecific cellular toxicity of the drugs [2, 4–7]. Among the long-term effects, secondary neoplasia is one of the most serious adverse effects. Many of the cytotoxic chemotherapeutic drugs used in current therapeutic regimen are known to show dose-dependent carcinogenic effects in animal models (see [8] for further references). The same is true for radiotherapy (RT) in humans [8]. But it is difficult to prove the carcinogenic effects in clinical studies due to the relatively small number of events, the lack of control groups and the routine use of multiagent therapies. Additionally, in cases with second-line therapies, competing risks of primary and relapse therapies complicate the analysis. Hence, assessing secondary neoplasias requires the pooling of large clinical studies with sufficiently long follow-up while generating only rough estimates of effects.

*Correspondence to: Dr M. Scholz, Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Haertelstrasse 16-18, Leipzig, 04107 Germany. Tel: +49-341-97-16190; Fax: +49-341-97-16100; E-mail: markus.scholz@imise.uni-leipzig.de

Secondary acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are the best-studied malignancies after chemotherapy [9]. These two entities are generally jointly considered because of similar etiology [10, 11]. Increased incidence of secondary AML/MDS is clearly related to the primary chemotherapy [10–14]. The AML/MDS-inducing effect of chemotherapy is assumed to be based on DNA-breaking alkylating agents (e.g. cyclophosphamide, procarbazine) and Topoisomerase II inhibitors (e.g. doxorubicin, etoposide) while the effect of RT is less clear [10, 11, 15–18].

Several study groups assessed the long-term incidence of AML/MDS for different primary therapies of Hodgkin’s lymphoma (see [19, 20] for an overview and meta-analysis). All published work agrees with respect to a low impact of RT alone on leukemogenic risk. Additionally, CT-induced leukemogenic risk depends on dose and kind of drugs [14, 21–24]. But there is disagreement about a modulating effect of combined CT + RT (CRT) compared with CT [21, 23, 24]. A meta-analysis showed increased risk after CRT compared with CT only for advanced stages [19].

Secondary non-Hodgkin’s lymphoma (NHL) is also observed after therapy of HL [25–28]. The risk of NHL proved to be significantly higher after HL therapy compared with normal population [8, 12, 27, 29, 30]. However, the causality between CT or RT and secondary NHL is less clear than for secondary AML/MDS. Other mechanisms such as evolution of HL, general immunodeficiency, common origin, misclassification of lymphoma, possibility of composite lymphoma or difficulties in delineation of lymphomas are also discussed [8, 29, 31–35]. Both CT and RT are suspected to induce secondary NHL since NHL incidence is also elevated after therapies of other cancers than HL or other reasons for RT [36, 37]. But the incidence of NHL is considerably higher after therapy of HL than after therapies of other cancers which could be a consequence of higher CT doses but also due to the factors mentioned above [37, 38]. A few studies tried to correlate treatment modalities with the risk of secondary NHL. Comparisons between RT alone, CT alone, CT + RT or chemotherapy dose were often negative [12, 19, 29, 39, 40] except for [30, 41]. Since all single studies had low case numbers, a meta-analysis has been carried out and showed no difference in incidence of NHL between CT and CRT. An effect of higher incidence of NHL after RT compared with CRT has been shown for early stages only [19].

The superimposing effects of first- and second-line therapy are rarely disentangled in the literature. The main analysis of Franklin et al. [19] included all events and observation times irrespective of relapse or progression of Hodgkin’s lymphoma, while in a secondary analysis, observation times were censored at relapse or progression.

One of us (ML) contributed to Tsodikov et al. [42, 43] proposing a statistical method to estimate the hazard functions of primary and relapse treatment and the competitive effect as well. This method is based on fitting a parametric statistical model of carcinogenesis to available data. The model has been underused probably because it is more complicate and respective software is not readily available in standard statistical packages. In the present paper, we aim to apply this method to data of the GHSG in order to answer the question whether

intensified radio-chemotherapy regimens (e.g. the novel BEACOPP escalated chemotherapy) increase the risk of secondary AML/MDS and NHL, respectively. Additionally, we aim to estimate the shapes of the hazard functions. We also propose a generic stepwise procedure to simplify the Tsodikov modeling approach as far as possible.

patients and methods

study population

The study population is based on eight randomized trials carried out by the German Hodgkin’s Lymphoma Study group from 1978 to 1998. It is essentially the same as described in [44, 45]. Only follow-up times are slightly longer. The Table 1 gives an overview of the studies and events. A review of all study results can be found in [46].

Studies were pooled according to severity of disease and corresponding intensity of therapy (Table 2). Patients were divided into four groups of primary treatment: RT only, therapy of intermediate stages (low dose chemotherapy and radiotherapy—iCRT), therapy of advanced stages (medium dose chemotherapy and radiotherapy—aCRT) and advanced stages treated with the dose-dense BEACOPP escalated regimen (BeCRT).

Treatments after disease progression or relapse were highly heterogeneous and not well documented throughout the studies and study arms. More than 400 different therapeutic interventions were found ranging from multiple myeloablative high-dose chemotherapy with stem cell transplantation over different chemotherapy and RT regimen to palliative care only. We decided to combine all these therapies to one additional risk factor of relapse therapy contributing to the overall secondary AML/MDS or NHL hazard.

model of carcinogenesis

The present analysis is based on a stochastic model of carcinogenesis after therapy of primary cancer proposed by Tsodikov et al. [42, 43]. The basic idea of the model is that a therapy can induce a carcinogenic lesion in a fraction of patients which results in a clinically apparent cancer with some time delay. Since a significant part of patients are not affected, resulting time to event curves show a long-term plateau. A concurrent risk assumption is made by modeling both primary therapy and, if applicable, secondary therapy of disease progression or relapse. Hereby, the hazard of the primary therapy is modified by the relapse treatment. The underlying biological motivation of this assumption is that existing lesions could be reduced or destroyed by the relapse treatment.

The hazard rate $h_p^j(t)$ of the primary treatment j at the time t is modeled as:

$$h_p^j(t) = \begin{cases} \log(\theta_p^j) f_p^j(t) & t < T_R \\ q_R \log(\theta_p^j) f_p^j(t) & t \geq T_R \end{cases}$$

where T_R is the time of relapse and $f_p^j(t)$ is a continuous probability density, which describes the shape of the hazard function after the primary treatment j . As discussed by Tsodikov et al., the gamma-family is chosen as a class of suitable shape functions for f .

Hence,

$$f(t) = \frac{b^a}{\Gamma(a)} t^{a-1} \exp(-bt), \quad \Gamma(a) = \int_0^\infty x^{a-1} \exp(-x) dx,$$

where the shape parameters a and b are again specific for each primary therapy and the relapse therapy as well. The parameter θ_p^j can be

Table 1. Study population grouped with respect to trial

Study	Therapies	Patients	Person-years	Median follow-up (months = days/30.44)	AML/MDS events	NHL events
HD1	2 × (COPP – ABVD) + RT	147	1654	142	1	6
HD3	3 × (COPP – ABVD) + RT (Arm A/C) 4 × (COPP – ABVD) (Arm B) 3 × (COPP – ABVD)+4 × CEVD (Arm D)	247	2652	144	5	6
HD4	RT	375	3291	107	3	7
HD5	2 × COPP – ABVD + RT (Arm A) 2 COPP/ABV/IMEP + RT (Arm B)	975	8306	106	9	11
HD6	4 × COPP – ABVD + RT (Arm A) 4 COPP/ABV/IMEP + RT (Arm B)	586	4446	102	8	12
HD7	RT (Arm A) 2 × ABVD + RT (Arm B)	627	4363	93	3	14
HD8	2 × (COPP – ABVD) + RT	1136	8013	95	15	17
HD9	4 × (COPP – ABVD) ± RT (Arm A), 8 × BEACOPP Baseline ± RT (Arm B) 8 × BEACOPP escalated ± RT (Arm C)	1264	9177	101	23	24
Total		5357	41 902	102	67	97

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; RT, radiotherapy.

Table 2. Pooling of studies with respect to intensity of therapy

Group	Studies	Patients	Person-years	Median follow-up (months = days/30.44)	AML/MDS events	NHL events
RT only	HD4, HD7 (Arm A)	686	5411	100	4	16
Intermediate stage CT + RT	HD1, HD5, HD7 (Arm B), HD8	2574	20 216	101	27	39
Advanced stage CT ± RT	HD3, HD6, and HD9 (Arm A + B)	1631	12 805	105	22	37
Advanced-stage BEACOPP escalated ± RT	HD9 (Arm C)	466	3470	101	14	5

AML, acute myeloid leukemia; CT, conventional chemotherapy; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; RT, radiotherapy.

interpreted as the total percentage of individuals who suffer from the secondary neoplasia and is called 'nonsurvivor fraction' in the following. The parameter q_R is a number between zero and one describing the reduction of the hazard of the primary therapy by a relapse treatment at time T_R .

Analogously, the relapse treatment contributes to the overall hazard by the rate $h_1(t)$:

$$h_R = \begin{cases} 0 & t < T_R \\ \log(\theta_R) f_R(t - T_R) & t \geq T_R \end{cases}$$

where the overall hazard $h^j(t)$ after the primary treatment j is the sum of $h_p^j(t)$ and $h_R(t)$. Finally, the survival function can be derived from the hazard rate by $\exp\left(-\int_0^T h^j(t) dt\right)$.

model inference and parameter estimation

According to Tsodikov et al., the carcinogenesis model presented above can be fitted to data by maximum-likelihood estimation. However, for each treatment, a set of three parameters (θ, a, b) must be estimated. Since the resulting high number of parameters limits the interpretability and precision of the model, we aim to simplify the model as far as possible. For

this purpose, we sketch a general strategy in the following which will be applied to our data set later.

Model simplification is done by evaluating Akaike's information criterion (AIC) for a set of meaningful statistical model hypotheses (see below). The Akaike criterion is defined as the sum of the maximal negative logarithmic likelihood and the number of model parameters [47]. The model with the smallest AIC can be interpreted as the model of choice because it represents the best compromise between accuracy and simplicity. Hence, model hypotheses resulting in smaller AIC are accepted. In our situation, the set of hypotheses reads as follows:

- H1:** Proportional hazard assumption for all primary therapies: that is, the parameters a and b can be assumed as identical for all primary therapies j ($a_p^j = a_p, b_p^j = b_p$ constant for all primary therapies j).
- H2:** If H1 can be assumed, test proportional hazard assumption for all primary and relapse treatments ($a_R = a_p, b_R = b_p$).
- H3:** $q_R = 1$: this assumes that the hazard of the primary therapy is not affected by the relapse treatment.
- H4:** $q_R = 0$: this assumes that the carcinogenic effect of the primary therapy can be neglected in case of a relapse treatment.
- H5:** θ_R^j are equal for all j . That is, there is no difference in carcinogenic outcome among the primary therapies ($\theta_R^j = \theta_R$ constant for all primary therapies j).

- H6:** If H5 is true, check whether $\theta_P = \theta_R$ can be assumed which implies that there are no differences in carcinogenic outcome among all primary and relapse therapies.
- H7:** If H5 is not true, check for which primary therapies there are differences in carcinogenic outcome.

All model evaluations are based on likelihood maximization under the corresponding hypotheses. The maximization is carried out with the ‘optim’ procedure of the statistical software package ‘R’ (www.r-project.org [48]). To avoid local optimization, the maximization procedure has been repeated 100 times with randomly selected initial points sampled from the parameter space.

After identification of the simplified model structure, the remaining model parameters were estimated analogously. 95% Confidence intervals (CIs) of parameters were determined by the rejection condition of the likelihood ratio test. Since corresponding intervals are multivariate CIs in the sense that all model parameters are allowed to change in order to define suitable ranges of a model parameter, the CIs of, e.g., two non-survivor fractions θ_0^j cannot directly be compared. To test whether, e.g., two non-survivor fractions are significantly different, one needs to calculate the CI of the difference separately by reparametrization.

R-scripts of our analysis are available after request.

results

secondary AML/MDS

We omitted the category RT only for AML/MDS risk analysis since the shape of the hazard function cannot be estimated with only four cases (see Discussion section). Hence, a total of 63 events were available for our analysis (see Table 1). Seventeen of them occurred after relapse therapy.

The model selection step resulted in a model of proportional hazard of primary therapies but not of primary and relapse therapies (supplemental Table S1, available at *Annals of Oncology* online). Carcinogenic effects of primary therapy can be neglected in case of relapse treatment. Nonsurvivor fraction of iCRT and aCRT but not BeCRT can be considered as equal (supplemental Table S1, available at *Annals of Oncology* online).

Model parameter estimates are provided in Table 3. Analysis revealed that the cumulative leukemogenic risk after iCRT or aCRT without relapse therapy is 1.5% (95% CI: 1.0% to 3.3%), while the same risk for BeCRT is 4.4% (95% CI: 2.2% to 10.5%, $P = 0.004$). The overall risk after relapse therapy is estimated to be 4.5% (95% CI: 2.6% to 7.2%) which is significantly higher than the risk after iCRT/aCRT ($P = 0.029$) but comparable to that after BeCRT ($P = 0.96$).

Comparison of model and data can be found in Figure 1. Hazard curves are also provided. The hazard curves after primary therapy reach their maximum at 3.4 years, while the hazard curve after the relapse therapy is much steeper and reaches the maximum after 1.8 years.

secondary NHL

A total of 97 events were available for analysis of secondary NHL (see Table 1). Twenty events occurred after a salvage or relapse therapy.

The model selection step resulted in a model of proportional hazard of both, primary therapies and relapse therapies. Effect of primary therapy can be neglected in case of relapse therapy.

Nonsurvivor fraction of primary RT, iCRT, aCRT and BeCRT can be considered as equal, while the nonsurvivor fraction after relapse therapy must be assumed as different (supplemental Table S2, available at *Annals of Oncology* online).

Model parameter estimates are provided in Table 4. Cumulative risk after primary therapy is estimated to be 2.9% (95% CI: 2.0% to 8.8%), while the risk after relapse treatment is 6.6% (95% CI: 3.7% to 21.3%, $P = 0.002$).

Comparison of model and data can be found in Figure 2. Hazard curves are also provided. The hazard curves have a shape close to an exponential distribution.

discussion

In the present paper, we used a stochastic model of carcinogenesis to assess the risk of secondary AML/MDS or NHL after different therapies of Hodgkin’s disease on the basis of a dataset of the German Hodgkin Study group. The model allows separating the risk of primary treatment schedules and relapse therapy. We showed that the novel BEACOPP escalated chemotherapy for the treatment of advanced stages results in 4.4% secondary AML, while the other conventional CT + RT have only a 1.5% risk of AML/MDS. The risk under BEACOPP escalated therapy is comparable with that after relapse therapy. While the hazards of the primary treatments can be considered as proportional, the hazard function after relapse therapy is steeper. In contrast, there are no differences with respect to secondary NHL risk among the primary treatments but the relapse therapy results again in higher secondary NHL risk compared with primary therapy.

Table 3. Parameter estimates for the AML/MDS model

Model characteristics	Value	
Maximum of -log(likelihood)	807.9463	
AIC	814.9463	
Model parameters	Estimate	95% CI
$\theta_P^{iCRT}, \theta_P^{aCRT} = \theta_P^{i/aCRT}$	0.0151	0.0099–0.0331
θ_P^{BeCRT}	0.0439	0.0223–0.1052
θ_R	0.0448	0.0264–0.0716
$\theta_P^{BeCRT} - \theta_P^{i/aCRT}$	0.0288	0.0074–0.0769
$\theta_R - \theta_P^{i/aCRT}$	0.0297	0.0077–0.0572
$\theta_R - \theta_P^{BeCRT}$	0.000961	-0.0616–0.0360
q_R	0 (set)	0–0.95
a_P	2.060	1.235–3.174
b_P	8.557×10^{-4}	2.057×10^{-4} – 1.677×10^{-3}
a_R	3.027	1.494–5.400
b_R	3.042×10^{-3}	1.063×10^{-3} – 6.078×10^{-3}

95% CI is based on the multivariate likelihood ratio test (see Methods section). Numbers in italics are derived model parameters for which the 95% CI must be determined separately. Symbols are as follows: θ fraction of patients with secondary AML/MDS, subscripts relate to primary or relapse therapy, respectively, superscripts relate to primary therapy; q describes the reduction of the hazard of the primary therapy by the relapse therapy a and b are the shape parameters of the hazard functions. AIC, Akaike’s information criterion; CI, confidence interval.

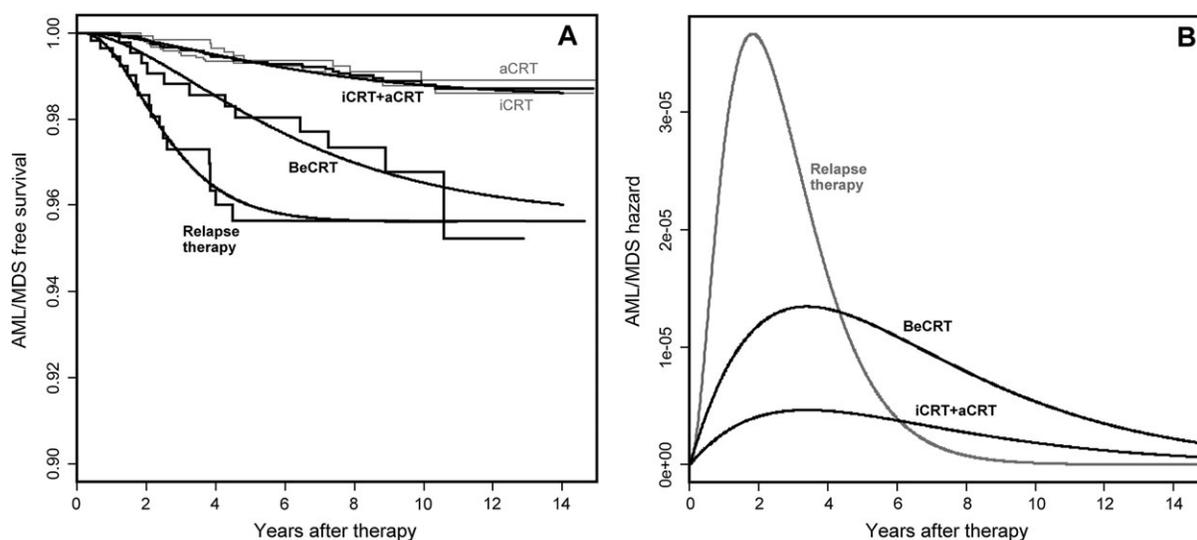


Figure 1. (A) Data (Kaplan–Meier estimates) and model survival curves (smooth curves) of the AML/MDS model. iCRT and aCRT were summarized. (B) Estimated parametric hazard curves.

Table 4. Parameter estimates for the NHL model.

Model characteristics		Value
Maximum of $-\log(\text{Likelihood})$		1241.414
AIC		1245.414
Parameter	Estimate	95% CI
θ_P	0.0285	0.0202–0.0884
θ_R	0.0657	0.0373–0.2127
$\theta_R - \theta_P$	0.0372	0.0108–0.1286
q_R	0 (set)	0–0.3498
a_P, a_R	1.051	0.774–1.390
b_P, b_R	3.711×10^{-4}	4.866×10^{-5} – 7.419×10^{-4}

95% CI is based on the multivariate likelihood ratio test (see Methods section). Numbers in italics are derived model parameters for which the 95% CI must be determined separately. Symbols are as follows: θ fraction of patients with secondary NHL, subscripts relate to primary or relapse therapy, superscripts relate to primary therapy; q describes the reduction of the hazard of the primary therapy by the relapse therapy; a and b are the shape parameters of the hazard functions.

AIC, Akaike's information criterion; CI, confidence interval.

For our analysis, it was necessary to pool eight randomized trials comprising different treatment protocols. Since a single randomized study is usually too small to prove any effects of therapy or other covariates, such pooling is unavoidable to answer clinically relevant questions [19, 37]. Our major aim was to investigate the dosing effect of chemotherapy. Therefore, we decided to roughly divide our study population into four groups of increasing total dose of CT: RT only, CT + RT of intermediate stages, CT + RT of advanced stages (except for BEACOPP escalated) and BEACOPP escalated. The chemotherapies applied for intermediate and advanced stages are diverse in dose and composition but were mostly COPP/ABVD like. The total doses applied for the advanced stages are always higher than for intermediate stages. The radiotherapies were also diverse with respect to dose and location throughout

all regimens. Almost all of our cases received additional RT which allows the estimation of leukemia risk of combined CT + RT therapy but not CT alone.

All relapse therapies were pooled. This might seem to be hazardous because of the large heterogeneity of relapse treatments. However, one can assume that all relapse therapies with curative aim are intense therapies, while palliative therapies result in early censoring of patients which does not influence our estimation of hazards.

We used a parametric model of carcinogenesis proposed by Tsoodikov et al. [43] to analyze our data. This approach has several advantages. Firstly, it offers the ability to model the superimposing risks of first- and second-line therapy. Furthermore, it allows arbitrary modifications of primary hazard by relapse therapy and allows for therapy-specific hazard functions. The separate analysis of the superimposing risks of primary and relapse therapy is necessary to obtain an unbiased estimate of the therapy-specific hazards. In published analyses, the relapse therapies are in general censored when assessing the risk of the primary therapies. Under this point of view, the method proposed by Tsoodikov et al. [43] is more subtle [19].

Because of the parametric nature of the model, it is easy to interpret and allows the direct determination of the shape of a hazard function which is otherwise difficult to estimate. To avoid an overfitting of the model, we proposed a set of meaningful hypotheses which could be checked before any parameter estimation. These hypotheses include proportionality of hazards, equality of survivor fractions and assumptions regarding the degree of concurrence of primary and relapse therapy. On the basis of these hypotheses, we selected the most parsimonious model. This approach reduces the number of parameters making interpretations easier and more reliable.

We used the gamma-family to model the shape of the hazard function. This family is highly flexible and results in either a monotonically decreasing hazard rate or a hazard rate with a single maximum and a subsequent plateau. This is in

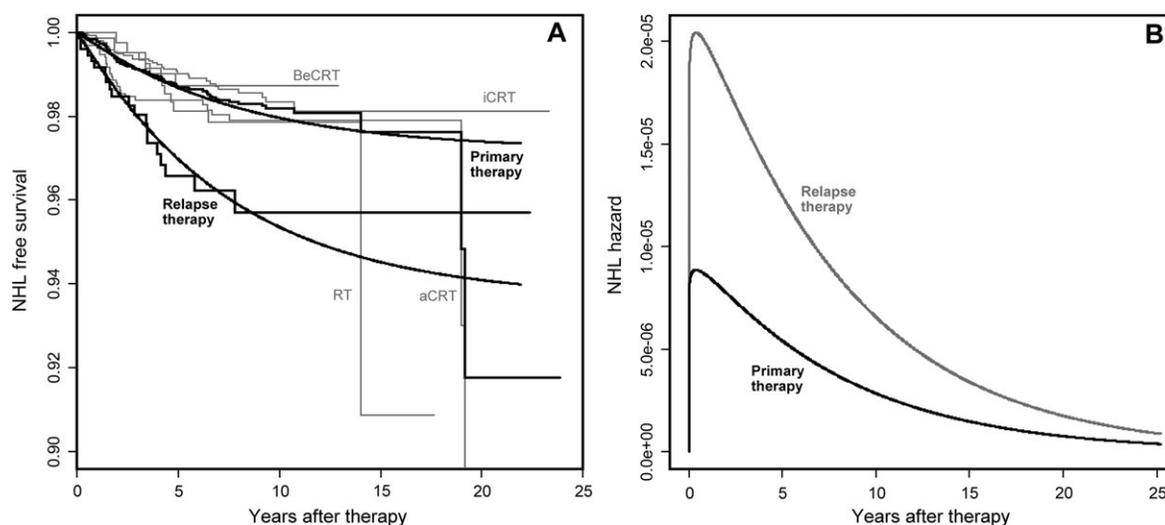


Figure 2. (A) Data (Kaplan–Meier estimates) and model survival curves (smooth curves) of the NHL model. All primary therapies were summarized. (B) Estimated parametric hazard curves.

accordance with most observations in literature [10, 11, 49]. In contrast, multiple maxima as claimed in [23] cannot be modeled with our approach but this seems to be not necessary in view of the good fit of our model and data.

The major findings of our AML/MDS model were that the AML/MDS risk after BeCRT was higher (4.4%) than after other conventional primary therapies (1.5%). This is in agreement with the paradigm that higher CT doses result in higher AML/MDS risk [10, 14, 21, 29, 38]. On the other hand, no differences were found between CRTs for intermediate or advanced stages, despite higher total case numbers. These therapies are mostly of COPP/ABVD type with varying numbers of cycles plus RT. The estimated total risk was in agreement with observations for ABVD [24].

One might speculate that increased doses of topoisomerase II inhibitors (etoposide and doxorubicin) in BeCRT are responsible for the increment in leukemic risk. This would fit well to the estimated hazard maximum at 3.4 years [11]. Alternatively, the dose-dependent increments in the other drugs may have been too small to detect a difference iCRT versus aCRT (roughly two courses COPP/ABVD or ABVD versus four courses), while the difference between iCRT + aCRT versus BeCRT was sufficiently detectable (e.g. about four times the dose of cyclophosphamide).

The overall risk of AML/MDS after relapse therapy was estimated to be comparable with that after BeCRT but the shape of the hazard was much steeper and the maximum was reached much quicker. This fits well into the context of a multiple-hit model of leukemogenesis proposed by Park & Koefler [10]. An alternative interpretation is that relapse patients are a selection of HL patients with increased risk for AML/MDS.

The risk of AML/MDS after RT only could not be estimated initially since the low event numbers are insufficient to estimate the shape of the hazard function. However, assuming proportional hazard of all first-line treatments and using the identified shape parameters of primary therapy and the

parameters of the relapse therapy as well, the AML/MDS risk after RT can be estimated in a *post hoc* analysis of our model. The risk was estimated to be low (0.88%, 95% CI: 0.22% to 2.28%) in accordance to literature.

For the NHL model, we find that the risk of the different primary treatment modalities can be assumed as equal (2.9%). This is in agreement with Tucker et al., Franklin et al., Swerdlow et al., Dietrich et al. and Enrici et al. [12, 19, 29, 39, 40] but in contrast with Bhatia et al. and van Leeuwen et al. [30, 41]. Since there are no effects of treatment modalities, one might speculate that the therapy has only a limited influence on secondary NHL risk and that these NHL cases instead have another origin [8, 29, 31–35]. The exponential shape of the hazard function supports this hypothesis. We found a clear increment of NHL risk after secondary treatment which could also be interpreted in the above context since the relapsed patients might be a selection of HL patients with increased NHL risk due to type of primary lymphoma or immune status.

Do our results influence treatment decisions? In our opinion, the primary issue is to cure the primary disease preferably without relapses in view of the high leukemia risk after relapse treatment [10, 21]. Recently published long-term follow-up data revealed that the gain in overall survival by BeCRT for advanced stage diseases clearly outweighs the increased incidence of leukemia [3]. Our findings contribute to the overall risk assessment of therapy and may help in developing less leukaemogenic treatment, especially for younger patients.

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disclosure

The authors declare no conflict of interest.

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