A CURE MODEL WITH TIME-CHANGING RISK FACTOR: AN APPLICATION TO THE ANALYSIS OF SECONDARY LEUKAEMIA

A report from the International Database on Hodgkin's Disease

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SUMMARY

A parametric model is used to investigate the latency time of leukaemia observed in patients treated for Hodgkin's disease. In specifying the treatment effect on leukaemia-free survival, account was taken of a fraction of long-term survivors and of time-changing risk associated with the relapse of the primary disease. The model is applied to data collected in the International Database on Hodgkin's Disease. It permits estimation of the contributions of primary and of relapse treatment to the overall risk of induced leukaemia. Baseline hazards appear to be identical after primary and relapse treatments supporting the concept that induced leukaemia have common origin. The probability to induce leukaemia by MOPP chemotherapy is the same, regardless whether used as primary or relapse treatment. © 1998 John Wiley & Sons, Ltd.


1. INTRODUCTION

The last decades have seen dramatic therapeutic progress in Hodgkin's disease (HD) resulting in about a 70 per cent cure rate.1,2 This success resulted from the introduction of new modalities of chemotherapy (CT) and/or radiotherapy (RT). The era of polychemotherapy and combined modality treatment has decreased the risk of HD-related death and at the same time increased the risk of second cancers.3,4 Acute myeloid leukaemia (AML) appears to be associated with HD therapy providing an up to 100 times higher risk in HD patients as compared with an age adjusted normal population.5

Many attempts have been made to evaluate this kind of risk by analyzing clinical data using the Cox model.1,4 Patients with Hodgkin's lymphoma are treated not only for the primary tumour

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but for its relapse as well. If therapy of the relapse influences the risk of leukaemia, the Cox model should be considered inappropriate, since the risks are no more proportional in this setting.

Quite flexible as it is, a non-parametric method does not allow projection of the leukaemia risk and other characteristics of the disease beyond the follow-up period. Since we were interested in risk prediction, a parametric approach has been used to separate the contributions of the primary treatment of HD and of the treatment of its relapse to the risk of leukaemia.

2. DATA AND PRELIMINARY REMARKS

In the subsequent analysis use was made of the International Database on Hodgkin’s Disease (IDHD) collected at 15 cancer centres and 5 co-operating groups (see Appendix). The data set includes records of about 13,000 newly diagnosed patients with HD treated between 1960 and 1987. Patients of all disease stages were included if older than 15 years. The majority of patients were less than 60 years of age. A wide variety of treatment strategies ranges from involved field irradiation in stage I to intensive combined modality treatment in stage IV. Over 85 per cent of the chemotherapy regimens used were MOPP-like not containing adriamycin. The records also contained follow-up data for each patient including date of relapse, death, cause of death, second neoplasia, and type of neoplasia. With a total of 82,850 person-years at risk, 631 second neoplasias have been reported: 106 non-Hodgkin lymphomas; 367 solid tumours, and 158 leukaemias (ICD 204–208). We restrict our attention to the latter.

We consider two groups of patients with respect to the type of treatment. Patients assigned to group 1 received radiotherapy alone (RT) as the primary treatment and MOPP-like chemotherapy (CT) if relapsed. Patients assigned to group 2 received MOPP-like primary CT and some chemotherapy (any type CT, denote by RCT) if relapsed. This classification contains 88 per cent of the whole cohort.

The group of patients (12 per cent) excluded from analysis was quite heterogeneous: 382 patients were treated by a single-agent CT (mainly in the 1960s); 858 patients received some CT which was not specified in the database (pooled into ‘unspecifed’ or ‘other type’), and 284 patients were treated by modern adriamycin containing regimens which are rumoured to be less leukaemogenic than MOPP. Since only a few leukaemia cases were observed in the excluded group, it is not possible to estimate the leukaemogenicity of various CT in this group. We therefore restrict ourselves to the subset group 1 + group 2 of the IDHD.

In what follows the group number (j) will be shown in brackets. A summary of the data is given in Table I.

A critical question is whether leukaemia is induced by CT and/or RT. A remark is in order that a higher incidence of leukaemia in HD patients as compared with an adjusted general population does not imply that leukaemias are induced by therapy. Possibly, those who develop HD might have an increased spontaneous rate of leukaemia. To clarify the issue we have to distinguish between spontaneous and induced leukaemia. From Table I we notice that the incidence of leukaemia prior to HD relapse is 7 times higher in patients primarily treated by RT than among those treated by MOPP CT. Although MOPP CT is more efficient in preventing relapses (20 per cent after MOPP CT versus 33 per cent after RT), the 7 times difference in leukaemia incidence prior to HD relapse is difficult to attribute just to a slightly better freedom from relapse distribution in group 2.
A CURE MODEL WITH TIME-CHANGING RISK FACTOR

Table I. A summary of the International Database on Hodgkin's Disease (IDHD)

<table>
<thead>
<tr>
<th></th>
<th>Group 1 RT + MOPP</th>
<th>Group 2 MOOP + RCT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD relapses</td>
<td>1777 (33%)</td>
<td>1223 (20%)</td>
<td>3000 (26%)</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>43 (0.8%)</td>
<td>109 (1.8%)</td>
<td>152 (1.3%)</td>
</tr>
<tr>
<td>Leukaemia prior to relapse</td>
<td>13 (0.2%)</td>
<td>87 (1.4%)</td>
<td>100 (0.9%)</td>
</tr>
<tr>
<td>Leukaemia after relapse</td>
<td>30 (0.6%)</td>
<td>22 (0.4%)</td>
<td>52 (0.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>5403 (100%)</td>
<td>6113 (100%)</td>
<td>11516 (100%)</td>
</tr>
</tbody>
</table>

![Graph](image)

Figure 1. Overall survivor function estimates for leukaemia in the two groups of patients (censoring excluded): 1a, the stratified life-table estimate in group 1; 1b, the parametric estimate (12) in group 1; 2a, the stratified life-table estimate in group 2; 2b, the parametric estimate (12) in group 2

The proportion of leukaemia observed in relapsed patients is about the same in both groups. We note that HD relapses are treated by CT in both groups. However, the patients of the second group have already received a CT treatment primarily. Therefore the potential of a CT treatment in this group is to a great extent exhausted and an aggressive (and heterogeneous) RCT is usually given if relapsed, which still provides a worse prognosis than in the relapsed patients of the first group.

Everything falls into place if we assume that leukaemia is induced by therapy. In the first group the majority of leukaemia cases are observed after MOPP CT of relapse, which fits the idea suggested by radiobiologists that irradiation predominantly induces solid tumours. Since RCT is

more aggressive than MOPP CT, it induces more leukaemias in the second group, which, however, have less time to develop because of a poorer prognosis. The two effects counteract to give about the same proportion of leukaemia in relapsed patients of the second group as observed after MOPP CT of relapse in the first group.

Another point in discriminating between induced and spontaneous leukaemia comes about from observing the S-shape and the plateau of leukaemia-free survivor curves (Figures 1 and 2). Spontaneous leukaemia can be thought of as developing from primary lesions induced in an individual according to some point process. The intensity of this process reflects the varying risk factors in the environment as well as the individual-specific status. If all other causes of death were removed, an individual would be expected to die from leukaemia, since the spontaneous formation of lesions never stops, and moreover its intensity is likely to increase with age. Therefore, the 'spontaneous' leukaemia-free curve is expected to be of the proper type and most likely with increasing hazard. Contrastingly, the 'induced' leukaemia-free curve is expected to have a positive plateau for large t, since leukaemia is most likely to be induced only in a small proportion of patients. The corresponding hazard function is not monotonic, because of the zero hazard for long-term survivors.

Yet another complication lies in the fact that CT or RT not only induces tumour cells but also kills them. Biologists suspect that the observed treatment effect results from a superposition of both effects. If a patient is treated twice (if relapsed), a possibility that the relapse therapy kills some of tumour cells induced by the primary treatment and thereby reduces its allied risk should be taken into account. As will be evident in Section 7, it is difficult to estimate this effect reliably even with such a large data set as IDHD.
3. BASIC MODEL

Given an inducing event at time $t = 0$ the survivor function is supposed to be of the form

$$
\overline{G}(t) = \exp\{-H(t)\}
$$

(1)

where $H(t)$ represents the cumulative hazard

$$
H(t) = \int_0^t h(x) \, dx
$$

$h(x)$ being the hazard function. Here and in what follows we understand that $\overline{Q} = 1 - Q$ for any function $Q$.

A survivor fraction implies an integrable hazard function and a bounded cumulative hazard $H(t)$ resulting in an improper $\overline{G}(t)$:

$$
H(t) \leq \theta, \quad \lim_{t \to \infty} H(t) = \theta.
$$

(2)

Consequently, the cumulative hazard can be represented in the form $H(t) = \theta F(t)$, where $F(t)$ is the distribution function of some non-negative random variable (RV)

$$
\overline{G}(t) = \exp\{-\theta F(t)\}.
$$

(3)

We may consider a regression model based on (3) if $\theta$ and/or $F$ depends on covariates.

4. ‘DEEP’ MODELS AND THE PROPORTIONAL HAZARDS ASSUMPTION

Using statistics to analyse biological data calls for hypothetical constructs which would explain the properties of the observed data. Such models are based on additional assumptions, which although plausible cannot be verified by the data. The justification for the use of such models lies not in an appeal to their ‘reality’ or otherwise but rather to the fact that these abstractions serve to synthesize and summarize the properties of observed data and to generate further hypotheses for which experimental evidence has to be collected. In this section we review some models which ‘explain’ expression (3) in a particular way and provide a link to interpretation of the analysis in Section 7.

Caveat should be advised with such models, since they allow the experimenter to impose preconceived ideas on the raw data. Causal relations can only be established through patient active manipulations and the analysis of various data sets.

4.1. Mixture models

There has been much earlier work to account for a survivor fraction (a probability of cure); see references 8, 9 and 10, to name a few. Most of the cure models assume an unobserved subpopulation of long-term survivors. To formulate it another way, an unobserved prognostic factor is considered which would allow classification of individuals as long-term survivors. The model then has the form of a mixture of distributions arising from integration with respect to the distribution of the unobserved factor (a mixing variable). A class of such frailty models arises if we consider a standard proportional hazards (PH) model and take the relative risk (unobserved individual’s susceptibility) as a mixing variable

$$
\overline{G}(t) = E\{\exp(-\nu H_0(t))\}
$$

where $H_0$ is the baseline cumulative hazard. A class of such models generated by a compound Poisson distribution for $\nu$ is considered by Aalen. A particular case of the model by Aalen arises if the compound Poisson distribution for $\nu$ degenerates into a Poisson one. It is easy to show that this particular model is matched to the expression (3) if $\theta = E\nu$ and $F(t) = 1 - \exp \{-H_0(t)\}$. In the next subsection this model will be interpreted as a simple model of induced carcinogenesis which serves to explain the presence of long-term survivors and the proportionality of hazards.

The mixture assumption is a strong one and should be used with caution as indicated in reference 8. Evidently, the mixture interpretation of (3) fails if the chance of cure is an outcome of an unknown stochastic process in time and the population is homogeneous at $t = 0$.

4.2. A simple model of carcinogenesis

Assume that the tumour originates from initial lesions in a patient. Let the number of such lesions $\nu$ be Poisson distributed with parameter $\theta$. We model the observed tumour onset time $U$ by independent competing risks associated with the lesions' progression

$$U = \min_{0 < k < \nu} X_k$$

(4)

where $X_0 \equiv \infty$, and $X_k$ are the independent and identically distributed progression times. Let $F$ be the distribution of the progression time. The tumour-free survivor function of a particular patient will be given by $[1 - F(t)]^\nu$. Since $\nu$ is unobservable we may repeat the frailty reasoning of the previous subsection and get

$$E[1 - F(t)]^\nu = \exp\{-\theta F(t)\}.$$ 

See references 6, 13, 14 and 15 for more details.

4.3. Proportional hazards (PH) assumption

The fact that the PH model has gained widespread acceptance in the analysis of time to tumour data calls for a biological explanation. The question that needs to be asked is why are the hazards proportional? The above model endows the PH assumption with a clear meaning: while the extent (and type) of HD therapy influences the number of induced lesions, the progression time distribution $F$ is shared by the treatment groups if all the lesions are of the same origin.

We may argue that the function $F$ gives rise to a PH family unique to a particular disease. We will be interested in testing the hypothesis that leukaemia induced by different HD therapies are of common origin. This does not imply the equality of the probabilities of leukaemia in different groups, hence we cannot apply homogeneity testing. If we assume that the effect of HD therapy follows a PH model we could identify this hypothesis with an overall test for proportional hazards.

If the probability of induced leukaemia is small ($\theta \to 0$) as estimated in Section 7, we will have a test for homogeneity for patients with leukaemia. Indeed, given induced leukaemia, the leukaemia-free survivor function $\bar{G}(t|\text{leukaemia})$ has the form

$$\bar{G}(t|\text{leukaemia}) = \frac{\exp\{-\theta F(t)\} - \exp\{-\theta\}}{1 - \exp\{-\theta\}}.$$ 

As $\theta \to 0$ we have $\bar{G}(t|\text{leukaemia}) \to F(t).$
Small $\theta$ can be interpreted as a proportion (a probability) of induced cancer in a simple mixture model

$$G(t) \approx \theta F(t), \text{ for small } \theta$$

$F$ being the time to tumour distribution among those who have induced cancer.

5. REGRESSION MODELS

The structure (3) allows us to consider covariates prognostic for $\theta$ and for $F$ separately. In particular we may consider a regression model

$$\tilde{G}(t|z) = \exp(-\theta(z) P(t|z))$$

(5)

where $z$ is a vector of covariates (we omit the index which would relate $z$ to a particular patient).

If $F$ were independent of $z$, the model (5) would be a PH model. This formulation calls for a likelihood which would allow estimation of the cure rates without having to estimate the other nuisance parameters ($F$) jointly. If the censoring is of type I, the probability of cure can be simply estimated by the proportion of censored observations from a homogeneous sample. Within the framework of the PH model under type I censoring, a marginal likelihood has been suggested which allows estimation of the cure rates,\textsuperscript{16} if covariate information is available. It is noteworthy that the rank's marginal likelihood no longer coincides with the Cox's partial likelihood if cure is a possibility. It is shown in reference 16 that the marginal likelihood outperforms the partial one and is practically as efficient as the parametric likelihood with small samples.

A parametric model of type (5) was considered in reference 17 to describe breast cancer recurrence. An advantage of the model (5) is that it allows for a classification of covariates as exerting a predominant influence on $\theta$, on $F$, or on both. For example, the CT/RT dose is expected to influence the extent of induction $\theta$, but not the leukaemia baseline function $F$, which is supposed to be unique to the disease.

We return to the example of Section 2. The treatment given to a patient will be coded by a pair $(i,j)$ as in Table II.

Consider a regression model for leukaemia induced by the primary therapy. Proceeding from the predictor in the exponential form $\theta(z) = \exp(\beta z)$ and assigning an indicator variable for each treatment option in Table II we get for a given patient with time to relapse $T_R$

$$\theta(z(t)) = \exp(\beta_0^{(j)} - \beta_1^{(j)} I(t - T_R))$$

(6)

where $\beta_1^{(j)}$ is a regression coefficient of the covariate as coded in Table II, and $I$ is an indicator function

$$I(x) = \begin{cases} 1, & x \geq 0, \\ 0, & x < 0. \end{cases}$$

The PH assumption related to primary treatment ($i = 0$) may not hold between treatment groups. Therefore a stratified model is considered by letting $F$ depend on covariates, so that for a patient in the treatment group $j$ we have $F(t|z) = F_0^{(j)}(t)$. The net hazard function $h_0$ related to primary therapy acquires the form of a PH model with a time-dependent ancillary covariate\textsuperscript{18} within a treatment group

$$h_0(t|z) = \begin{cases} \theta_0^{(j)} f_0^{(j)}(t), & t \leq T_R \\ \theta_0^{(j)} \delta_1^{(j)} f_0^{(j)}(t), & t > T_R \end{cases}$$

(7)

Table II. Coding of treatment $(i, j)$, $i = 0, 1; j = 1, 2$

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary treatment</td>
<td>(0, 1)</td>
<td>(0, 2)</td>
</tr>
<tr>
<td>Relapse treatment</td>
<td>(1, 1)</td>
<td>(1, 2)</td>
</tr>
</tbody>
</table>

where $f_0^{(j)}$ is the density corresponding to $F_0^{(j)}$, $\theta_0^{(j)} = e^{-\beta_0}$ describes the initial effect of primary treatment; and $q_1^{(j)} = e^{-\beta_1} \leq 1$ describes the post-relapse effect of primary treatment.

Model (7) is commonly used to describe survival in a population subject to an acute change of hazard occurring at a random time point (see references 19 and 20 for an example on bone marrow transplantation).

To understand the qualitative meaning of coefficients $\theta_0^{(j)}$ and $q_1^{(j)}$, a mechanistic interpretation might be of help. Let us recall the model (4) and assume that a leukaemia lesion $(k)$ latent at time $T_R$ of HD relapse ($X_k > T_R$) is cured by the relapse therapy with a probability $\tilde{q} = 1 - q$. It is easy to show that the above model yields (7), where $f_0^{(j)}$ is the distribution density of the progression time of a lesion induced by primary therapy in group $j$. We thus arrive at the mechanistic interpretation of (7) with:

$\theta_0^{(j)} = \text{the mean number of lesions induced by the primary therapy in the treatment group}$

$j = \text{the probability to induce leukaemia by the primary therapy (if small)}$

$q_1^{(j)} = \text{the probability that a latent lesion (latent leukaemia) survives the therapy of HD relapse}$

Similarly, the net hazard function $h_1$ related to leukaemia induction by the relapse therapy is modelled by

$$h_1(t|x) = \begin{cases} 0, & t < T_R \\ \theta_1^{(j)} f_1^{(j)}(t - T_R), & t \geq T_R. \end{cases}$$

Assume that leukaemia risks associated with the primary and the relapse therapies are independent given the covariates. Combining (7) and (8) we get the competing risks model

$$h(x|z) = h_0(t|x) + h_1(t|x).$$

It might be well to point out that because of the shift $T_R$ in the function $f_1^{(j)}$ the model (9) cannot be made a PH one by pooling the baseline functions across strata $F_0^{(j)} = F$, $i = 0, 1; j = 1, 2$.

The weak model (9) can be used as a starting point for model selection and testing the goodness-of-fit. Two hypotheses seem reasonable in this respect:

I. The baseline functions of induced leukaemia do not depend on when and by which therapy it is induced: $F_0^{(j)} = F$, $i = 0, 1; j = 1, 2$. This would suggest the common origin of induced leukaemia under the assumption that $F$ in unique to the disease.

II. The probability to induce leukaemia by MOPP CT is the same, whether used as primary or relapse treatment:

RT: $\theta_0^{(1)} = \theta_{RT}$

MOPP: $\theta_0^{(2)} = \theta_1^{(1)} = \theta_{MOPP}$

RCT: $\theta_1^{(2)} = \theta_{RCT}$.
6. ESTIMATION PROCEDURE

To provide a parametric representation of \( h(t|z) \), we need to specify the form of the functions \( f_{i}^{(j)} \). For mathematical convenience and because of its flexibility we choose the \( \Gamma \)-family

\[
 f(t) = \frac{b^{a}}{\Gamma(a)} t^{a-1} e^{-bt}
\]

and relate the parameters \( a, b \) to patient's covariates to get \( a_{i}^{(j)}, b_{i}^{(j)}, i = 0, 1; j = 1, 2 \). We have checked by simulations that the \( \Gamma \)-distribution fits well in the framework of carcinogenesis modelling.\(^{21}\) The shape parameter \( a \) and scale parameter \( b \) are related to the mean \( M \), and the standard deviation, \( \sigma \), of the progression time in the following way: \( M = a/b, \sigma = \sqrt{a/b} \). Because of the clear meaning we will use \( M \) and \( \sigma \) instead of \( a \) and \( b \) to identify the function \( f \).

Under non-informative censoring the likelihood can be written as

\[
 \ell = - \sum_{i, \text{all patients}} \int_{0}^{t_{i}} h(t|z_{i}) \, dt + \sum_{i, \text{uncensored}} \log h(t_{i}|z_{i}) \tag{10}
\]

where \( z_{i} \) is the covariate (treatment history up to \( t_{i} \)) of the \( i \)th patient and \( \{t_{i}\} \) is the sample of times to leukaemia or last news.

To obtain the ML estimates the likelihood (10) is maximized with respect to the unknown parameters

\[
 \max_{\theta^{(j)}, \phi^{(j)}, \alpha^{(j)}, \beta^{(j)}} \ell \tag{11}
\]

\[
 \theta_{i}^{(j)} > 0, \quad 0 \leq q_{i}^{(j)} \leq 1, \quad a_{i}^{(j)} > 0, \quad b_{i}^{(j)} > 0, \quad i = 0, 1; j = 1, 2.
\]

To maximize the likelihood, we use the random search maximization described in reference 15 to get the initial approximation in the domain of global maximum and the Powell algorithm\(^{12}\) to get the final solution.

It can be easily imagined that model (9) would be overfitted should all the variables in (11) be included. We use a backward exclusion procedure. This is organized by testing meaningful hypotheses on the linkage between the parameters, the hypotheses I and II of the previous section above all.

By solving (11) we get the ML estimate for the survivor function \( \tilde{G}(t|x) = \exp\{-\int_{0}^{t} h(u|x) \, du\} \) conditional on the treatment history \( x \). To indicate explicitly the dependence of \( \tilde{G}(t|x) \) on the time to relapse \( T_{R} \) and on the treatment group \( j \) we will write \( \tilde{G}(t|j, T_{R}) \). Denote \( \tilde{G}(t|j) \) the population survivor function in the treatment group \( j \). It is of immediate interest to estimate \( \tilde{G}(t|j) \), as far as predictions of the overall incidence of secondary cancer by treatment group are concerned. Let \( R_{j}(t) \) be the distribution of the time to HD relapse in the treatment group \( j \). Then

\[
 \tilde{G}(t|j) = \int G(t|i, t_{k}) \, dR_{j}(t_{k}).
\]

We estimate \( R_{j}(t) \) by the life-table method with secondary cancers considered as censoring events with respect to the time to HD relapse. The sought-for overall survivor function \( \tilde{G}(t|j) \) can then be estimated by

\[
 \tilde{G}(t|j) = \sum_{k=1}^{k} \tilde{G}(t|j, \tau_{k}) \Delta R(t|j, \tau_{k}) + \tilde{G}(t|j, \infty) \tilde{R}(t|j) \tag{12}
\]
where $t_k, k = 1, \ldots, n$ are the step-points of the life-table estimate; $\Delta R^{(j)}(t_k) = \bar{R}^{(j)}(t_{k-1}) - \bar{R}^{(j)}(t_k)$.

It can be shown that the predicted proportion of induced secondary cancers (censoring removed) by treatment group is given by

$$G^{(j)}(t) = 1 - \exp(-\bar{g}^{(j)}(t)) \left\{ \bar{R}^{(j)}(t) + \exp(-\bar{g}^{(j)}(t)) \sum_{k=1}^{n} \Delta R^{(j)}(t_k) \exp \left[ \bar{g}_0^{(j)} t \right] \right\}.$$  \hspace{1cm} (13)

To verify the parametric estimate $G^{(j)}(t)$, it will be compared with the non-parametric one. To do that we replace $\bar{G}(t_j, t_k)$ in (12) by a life table leukemia-free survivor curve computed for patients of group $j$ who have HD relapse in the interval $[t_{k-1}, t_k]$ (or who do not relapse at all for $\bar{G}(t_j, \infty)$).

To get an impression of identifiability we may consider an approximate procedure. In doing so, consider HD relapses as censoring events with respect to leukemia. In this setting only the information on leukemia induced by primary therapy is available, and a simple model like (3) can be fitted in each group to estimate the parameters related to primary therapy. After that, a population of relapsed patients may be considered with the conditional residual risk of primary therapy (given no leukemia prior to relapse) being replaced by its estimate obtained at the previous step. From the sample of relapsed patients we can estimate the risk of relapse therapy and $\alpha$. If $\alpha = 0$ as estimated in Section 7 (leukemia induced by primary therapy is eradicated by the relapse therapy), the approximate solution would coincide with the result of ML estimation.

It is clear that the parameters related to the relapse treatment may interact with $\alpha$ 'explaining' the incidence of leukemia after HD relapse by the influence of the relapse therapy or by the residual effect of primary therapy (if $\alpha > 0$).

7. COMPUTATIONS

Proceeding from the general model (9) we get the estimates as given in Table III. Observing the similarities in parameter values related to cumulative hazards $F_i^{(j)}, j = 1, 2, i = 0, 1$ one would suspect that $F_i^{(j)} = F, j = 1, 2, i = 0, 1$ (hypothesis I). The likelihood ratio test does not reject the hypothesis ($p = 0.65$). Next, the values of $\theta_1^{(1)}$ and $\theta_0^{(2)}$ are very similar (see Table III, estimates under hypothesis I) suggesting a natural further hypothesis that the extent of leukemia induction by MOPP CT is therapy-specific and does not depend on whether MOPP is used as primary or relapse treatment: $\theta_1^{(1)} = \theta_0^{(2)} = \theta_{MOPP}$ (hypothesis II). The hypothesis was accepted ($p = 0.69$). Compared with the non-parametric estimate, the model fits well (Figures 1 and 2).

This step appears to be the final decision, and the hypothesis $\theta_{MOPP} = \theta_{RCT}$ was rejected ($p = 0.006$). We are at the point to draw some conclusions:

(a) The baseline hazards related to inducing events are the same, suggesting that induced leukemias are of the same origin irrespective of the therapy under the assumption that $F$ is unique to the disease. The median duration of leukemia latency was estimated to be 6 years (mean = 7 years).

(b) RT-associated leukemia risk is very small compared with that of CT (see also Figures 2 and 3). The probability to induce leukemia by MOPP CT is the same, regardless whether used as primary or relapse treatment. Perhaps this property can be generalized to other types of CT/RT.

(c) RCT induces twice as many leukemia as the MOPP CT ($1 - e^{-\theta_{MOPP}} \approx \theta_{MOPP} \approx \theta_{RCT}/2$), see also Figure 2.
Table III. Estimated model parameters under various hypotheses. $\sigma$ and $M$ are measured in months. Confidence intervals (likelihood ratio) for the final solution are shown in brackets

<table>
<thead>
<tr>
<th></th>
<th>General model (9)</th>
<th>(9) under hypothesis I $F^{(i)} = F$</th>
<th>(9) under hypotheses I and II $\theta^{(i)}_1 = \theta^{(i)}<em>2 = \theta</em>{MOPP}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\sigma^{(i)}_1$</td>
<td>$M^{(i)}_1$</td>
<td>$\theta^{(i)}_1$</td>
</tr>
<tr>
<td>Primary treatment (RT)</td>
<td>150</td>
<td>159</td>
<td>0.0072</td>
</tr>
<tr>
<td>Group 1 ($i = 0, j = 1$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse treatment (MOPP)</td>
<td>54</td>
<td>88</td>
<td>0.041</td>
</tr>
<tr>
<td>Group 1 ($i = 1, j = 1$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary treatment (MOPP)</td>
<td>50</td>
<td>80</td>
<td>0.0035</td>
</tr>
<tr>
<td>Group 2 ($i = 0, j = 2$)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Relapse treatment (RCT)</td>
<td>46</td>
<td>71</td>
<td>0.063</td>
</tr>
<tr>
<td>Group 2 ($i = 1, j = 2$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$p$-value</td>
<td>–</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
These conclusions should be treated with caution as a suggestion rather than as strong evidence. In addition to the discussion in Section 4 it should be stressed that the large p-values in the above computations indicate solely that the hypotheses I and II are compatible with the data, perhaps due to small numbers of leukaemia cases, particularly of those related to RT. The model also suggests that latent leukaemia is eradicated by the relapse therapy. This finding is extreme. To find out if the conclusions are stable with respect to a misspecified \( q \) we forced the reverse assumption \( q_1^{(j)} = 1, j = 1, 2 \). The hypotheses

\[
\begin{align*}
[1] & \quad F_i^{(j)} = F, \quad j = 1, 2, \quad i = 0, 1 \quad (p = 0.47) \\
[2] & \quad \theta_i^{(1)} = \theta_0^{(2)} = \theta_1^{(2)} = \theta_{CT} \quad (p = 0.98)
\end{align*}
\]

were accepted resulting in the following estimates:

<table>
<thead>
<tr>
<th>( \sigma ) (months)</th>
<th>( M ) (months)</th>
<th>( \theta_{RT} )</th>
<th>( \theta_{CT} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 (53, 69)</td>
<td>91 (82, 98)</td>
<td>0.0054 (0.0029, 0.0087)</td>
<td>0.038 (0.030, 0.046)</td>
</tr>
</tbody>
</table>

Comparing these estimates with Table III we notice that all parameters remain the same except for \( \theta_{RT} \) which was reduced to the \( \theta_{MOPP} \) level, and the conclusions (a) and (b) are still valid. If the likelihood ratio on testing the hypothesis \( q_1^{(j)} = 1, j = 1, 2 \) were \( \chi^2 \)-distributed we would get a non-significant result \( (p = 0.20) \).

In view of the above we have to admit that the estimate of \( q \) is perhaps unreliable even with such a large data set as IDHD. The conclusion (c) should be relaxed: RCT induces at least as many leukaemia as the MOPP CT.
The overall fraction of induced leukaemia was found (using (13)) to be 0.018 in group 1 and 0.049 in group 2. If a 10-times less leukaemogenic CT was available as the primary therapy in group 2, it would reduce the predicted leukaemia incidence only by a factor of 2. Since such an improvement on the aspect is unlikely, only a moderate success in reducing this severe long-term toxicity is to be expected from modern CT modalities, particularly in patients with advanced disease.

APPENDIX: LIST OF STUDY CENTRES AND PRINCIPAL INVESTIGATORS INVOLVED IN THE IDHD


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