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Evaluating joint effects of induction–salvage treatment regimes on overall survival in acute leukaemia

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Summary. Typical oncology practice often includes not only an initial front-line treatment but also subsequent treatments given if the initial treatment fails. The physician chooses a treatment at each stage based on the patient's baseline covariates and history of previous treatments and outcomes. Such sequentially adaptive medical decision-making processes are known as dynamic treatment regimes, treatment policies or multistage adaptive treatment strategies. Conventional analyses in terms of front-line treatments that ignore subsequent treatments may be misleading, because they actually are an evaluation of more than front-line treatment effects on outcome. We are motivated by data from a randomized trial of four combination chemotherapies given as front-line treatments to patients with acute leukaemia. Most patients in the trial also received a second-line treatment, which was chosen adaptively and subjectively rather than by randomization, either because the initial treatment was ineffective or the patient's cancer later recurred. We evaluate effects on overall survival time of the 16 two-stage strategies that actually were used. Our methods include a likelihood-based regression approach in which the transition times of all possible multistage outcome paths are modelled, and estimating equations with inverse probability of treatment weighting to correct for bias. Although the two approaches give different numerical estimates of mean survival time, they lead to the same substantive conclusions when comparing the two-stage regimes.

Keywords: Causal inference; Clinical trial; Dynamic treatment regime; Treatment policy

1. Introduction

Confirmatory evaluation of a new cancer treatment often is based on a randomized clinical trial with overall survival (OS) time as the primary end point. Compared with intermediate outcomes that may be used because they are observed sooner, such as disease-free survival time or tumour response, the OS time is widely considered to be the 'gold standard' for treatment evaluation because prolonging survival is the ultimate goal of cancer therapy. A fundamental problem with this paradigm is that, in typical oncology practice, a patient receives not only an initial, front-line treatment but also one or more subsequent treatments, chosen adaptively by the physician on the basis of the patient's history of treatments and outcomes. Each patient's OS time may depend on the entire sequence of treatments and the adaptive manner in which they were chosen, rather than only the front-line treatment. Consequently, a conventional statistical

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analysis of front-line treatment effects on OS that ignores subsequent treatments actually is an evaluation of more than just the front-line treatments.

This type of sequentially adaptive medical decision-making process is known as a dynamic treatment regime, treatment policy or multistage treatment strategy. There is a substantial statistical literature on methods for analysing observational data having this structure (Robins, 1986, 1997, 2004; Robins and Rotnitzky, 1992; Robins *et al.*, 2008; Murphy *et al.*, 2001; Lunceford *et al.*, 2002; Murphy, 2003; Wahed and Tsiatis, 2004, 2006). There also is a growing literature on methods for designing clinical trials to evaluate dynamic treatment regimes (Lavori and Dawson, 2000, 2004; Thall *et al.*, 2000, 2002, 2007; Murphy, 2005; Zhao *et al.*, 2009).

The problem that motivates this paper, and that will play a central role in determining our models and analytical methods, arises from the therapeutic decisions that oncologists make when a patient's front-line treatment has failed. In such cases, it is common clinical practice to administer a second-line, 'salvage' treatment that is different from the patient's front-line treatment. The data set that we shall analyse arose from a randomized trial of four combination chemotherapies given as front-line treatments to patients with poor prognosis acute myelogenous leukaemia (AML) or myelo-dysplastic syndrome (MDS). Chemotherapy of AML or MDS proceeds in stages. A 'remission induction' chemotherapy combination is given first, with the aim of achieving a complete remission (CR), which is defined as the patient having less than 5% blast cells, a platelet count greater than 10^5 mm^{-3} and white blood cell count greater than 10^3 mm^{-3}, based on a bone marrow biopsy. If the induction chemotherapy does not achieve a CR, or a CR is achieved but the patient suffers a relapse, then salvage chemotherapy usually is given in a second attempt to achieve a CR. The AML–MDS trial used a 2×2 factorial design with chemotherapy combinations fludarabine plus cytosine arabinoside plus idarubicin (FAI), FAI plus all-trans-retinoic acid (ATRA), FAI plus granulocyte colony stimulating factor (GCSF) and FAI plus ATRA plus GCSF. The primary aim was to assess the effects of adding ATRA, GCSF or both to FAI on the probability of success, which was defined as the patient being alive and in CR at 6 months. Analyses of this data set have been reported previously (Estey *et al.*, 1999), using conventional methods including logistic regression, Kaplan–Meier estimates and Cox model regression, assuming that the only relevant treatments were the front-line therapies.

Consideration of both front-line and salvage therapies leads to a far more complex picture of the interplay between treatments and outcomes. The possible pathways that a patient's actual course of therapy may have taken in the trial are illustrated in Fig. 1, which shows that a patient may die

(a) during induction therapy,

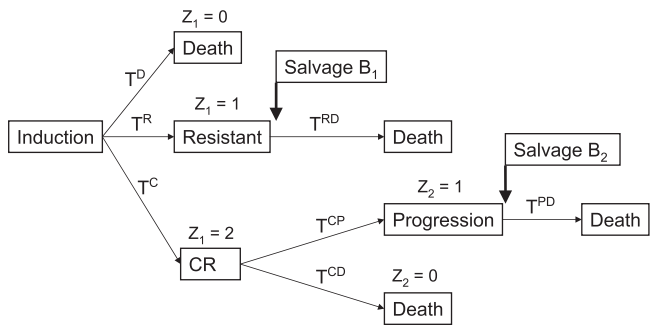

Fig. 1. Possible pathways of successive states, transition times and salvage therapy following induction treatment in acute leukaemia patients

(b) following salvage therapy given if the disease is resistant to induction,
(c) while in CR or
(d) following disease progression after CR.

The reasons for these different types of death are complex. For example, a patient might die while in CR because of cumulative damage to the patient's immune system and internal organs from either the chemotherapy or the leukaemia, or both.

Our primary goal is to evaluate the effects of (induction, salvage) strategies on OS. To do this, we shall keep track of all transition times between states (Fig. 1). We characterize treatment regimes by the triple $d = (A, B_1, B_2)$, where A denotes induction therapy, B_1 denotes salvage therapy for patients whose disease was resistant to induction and B_2 denotes salvage therapy for patients with disease progression following a CR achieved with induction. For regime (A, B_1, B_2), each patient received A only, (A, B_1) or (A, B_2). We shall discuss this point further in Section 2. We focus on regimes rather than individual treatments because the optimal regime $d^{\text{opt}} = (A, B_1, B_2)^{\text{opt}}$ may not correspond to what would be obtained by optimizing A, B_1 and B_2 separately at each stage of therapy. A common example in AML–MDS is that an aggressive front-line treatment may maximize Pr(CR), but it also may cause so much damage to the patient's immune system that a rapid relapse is likely and any salvage therapy B_2 given after relapse is unlikely to achieve a second CR. For example, suppose that two induction regimens, $A^{(1)}$ and $A^{(2)}$, both provide 12-month mean OS if CR is achieved, $\Pr(\text{CR}|A^{(1)}) = 0.60$ and $\Pr(\text{CR}|A^{(2)}) = 0.40$, and both have induction death probabilities 0.10. Although this suggests that $A^{(1)}$ is greatly superior to $A^{(2)}$, if $A^{(1)}$ is more immunosuppressive so that any salvage regimen B_1 given following resistance to $A^{(1)}$ has 2-month mean OS compared with 12 months with salvage following resistance to $A^{(2)}$, then the overall mean OS is $0.60 \times 12 + 0.30 \times 2 = 7.8$ months for $(A^{(1)}, B_1, B_2)$ and $0.40 \times 12 + 0.50 \times 12 = 10.8$ months for $(A^{(2)}, B_1, B_2)$. For treating solid tumours, a particular front-line chemotherapy A may be suboptimal as front-line chemotherapy to eradicate the tumour but have a high probability of debulking the tumour so that it is surgically resectable. Thus, the strategy (A, surgery) may be optimal to maximize OS. Such synergies may have profound implications for clinical practice, since a physician giving A^{opt} determined by considering only front-line treatments may unknowingly be setting patients on pathways that include only inferior regimes.

In the AML–MDS trial, patients were randomized between the four induction combinations to choose A, whereas the salvage treatments B_1 and B_2 were chosen subjectively by the attending physicians patient by patient. Consequently, considering the multicourse structure of the patients' actual therapy, the data are observational because salvage treatments were not chosen by randomization. This motivates our use of inverse probability of treatment weighted (IPTW) estimation (Robins *et al.*, 2000), which accounts for the variation in receiving a specific treatment by weighting each observation by the inverse of the propensity (estimated probability) of receiving that treatment.

In Section 2 we describe the data structure and establish notation for the outcomes, treatment regimes and likelihoods. Families of parametric models for the transition times are given in Section 3. Analyses of the AML–MDS data aimed at estimating the effects of treatment regimes on OS are given in Section 4, including both a model-based approach and the use of estimating equations. The results are contrasted with those of conventional analyses that ignore salvage therapy. We close with a brief discussion in Section 5.

2. Data structure and likelihoods

To provide a framework for analysing the treatment regimes that were actually used in the

AML–MDS trial, we first establish notation for the transition times and their likelihoods. As shown by Fig. 1, at the start of therapy the three possible events {death without the patient's disease being declared resistant or achieving CR}, {disease resistant to induction treatment} and CR are competing risks, since at most one can occur. We denote the respective times to these events from the start of induction by T^{D}, T^{R} and T^{C}. To keep track of which event occurred, denoting $a \wedge b = \min\{a, b\}$, we define $Z_1 = 0$ if $T^{\mathrm{D}} < T^{\mathrm{R}} \wedge T^{\mathrm{C}}$, $Z_1 = 1$ if $T^{\mathrm{R}} < T^{\mathrm{D}} \wedge T^{\mathrm{C}}$ and $Z_1 = 2$ if $T^{\mathrm{C}} < T^{\mathrm{D}} \wedge T^{\mathrm{R}}$. The transition time from the patient's disease being declared resistant to death is denoted by T^{RD}, which is defined only if $Z_1 = 1$. For patients whose induction therapy achieved a CR, subsequent progressive disease and death in CR are competing risks; the transition times to these events are denoted by T^{CP} and T^{CD}, and we define the indicator $Z_2 = I(T^{\mathrm{CP}} < T^{\mathrm{CD}})$ to record which of these two events occurred after CR. The transition time from disease progression to death is T^{PD}, which is defined only if $Z_2 = 1$. Similarly, T^{CP}, T^{CD} and Z_2 are defined only if $Z_1 = 2$. The distinction between a variable being well defined and being potentially observable is important. For example, the potentially observable variable T^{R} is not defined if $Z_1 = 0$.

Aside from discontinuation of therapy due to a reason other than death, including administrative right censoring or dropout, each patient's observed sequence of transition times consisted of exactly one of the four vectors (T^{D}), $(T^{\mathrm{R}}, T^{\mathrm{RD}})$, $(T^{\mathrm{C}}, T^{\mathrm{CP}}, T^{\mathrm{PD}})$ or $(T^{\mathrm{C}}, T^{\mathrm{CD}})$, with Z_1 the only outcome variable observed for all patients. The seven transition times, Z_2 and these four vectors may be thought of as counterfactual outcomes (Holland, 1986), in the sense that together they describe all possible outcome paths but each patient had only one outcome. Each patient's OS time may be expressed formally as follows:

$$T = \begin{cases} T^{\mathrm{D}} & \text{if } Z_1 = 0, \\ T^{\mathrm{R}} + T^{\mathrm{RD}} & \text{if } Z_1 = 1, \\ T^{\mathrm{C}} + T^{\mathrm{CP}} + T^{\mathrm{PD}} & \text{if } Z_1 = 2 \text{ and } Z_2 = 1, \\ T^{\mathrm{C}} + T^{\mathrm{CD}} & \text{if } Z_1 = 2 \text{ and } Z_2 = 0. \end{cases} \tag{1}$$

Tables 1 and 2 summarize the counts and median transition times for the seven possible events illustrated in Fig. 1 for the leukaemia data. These include the three induction therapy outcomes (indexed by Z_1) for each treatment arm and the four possible subsequent outcomes. Because there were many different salvage treatments, we classified salvage as either containing high dose arabinoside cytosine (HDAC) or not. The small discrepancy between

Table 1. Summary of outcomes following induction and salvage therapy by front-line treatment†

Group	*Initial outcomes following induction therapy*						*Total, N*
	Death		*Resistant disease*		*CR*		
	N (%)	T^{D} *(days)*	*N (%)*	T^{R} *(days)*	*N (%)*	T^{C} *(days)*	
All patients	69 (33)	$_{22}24_{32}$	39 (19)	$_{51}59_{70}$	102 (48)	$_{30}32_{34}$	210
FAI	17 (31)	$_{21}27_{52}$	17 (31)	$_{41}63_{97}$	20 (37)	$_{29}31_{44}$	54
FAI + ATRA	15 (28)	$_{18}22_{44}$	13 (24)	$_{55}59_{76}$	26 (48)	$_{29}31_{44}$	54
FAI + GCSF	20 (38)	$_{22}32_{45}$	4 (8)	$_{27}77_{112}$	28 (54)	$_{29}36_{40}$	52
FAI + GCSF + ATRA	17 (34)	$_{14}21_{30}$	5 (10)	$_{48}51_{70}$	28 (56)	$_{28}32_{38}$	50

†The sample median of each transition time is given, with lower and upper 95% confidence interval limits subscripted on the left and right.

Table 2. Summary of outcomes following induction and salvage therapy overall†

Group	*Outcomes following CR or resistant disease*							
	Death after resistant disease		*Death in CR*		*Progression after CR*		*Death after progression*	
	N (%)	T^{RD} *(days)*	*N (%)*	T^{CD} *(days)*	*N (%)*	T^{CP} *(days)*	*N (%)*	T^{PD} *(days)*
All patients	37 (95)	$_{62}79_{148}$	9 (9)	$_{46}293_{345}$	93 (91)	$_{190}256_{329}$	83 (93)	$_{106}128_{175}$
HDAC	25 (93)	$_{27}65_{117}$	—	—	—	—	47 (89)	$_{62}98_{253}$
Other treatment	12 (100)	$_{82}130_{252}$	—	—	—	—	36 (90)	$_{122}158_{191}$

†The sample median of each transition time is given, with lower and upper 95% confidence interval limits subscripted on the left and right.

the treatment arm sample sizes in Table 1 and those reported by Estey *et al.* (1999), Table 1, are due to exclusion of five ineligible patients and correction of two patients' treatment assignments. Although Table 1 does not account for covariates, it shows the generally poor outcomes in that only 48% of patients achieved a CR whereas 33% died during induction therapy, with this type of death very likely to occur in less than 2 months. The times to achieve CR or for the patient's disease to be declared resistant to induction were similarly short, with all patients' initial outcomes almost certainly known within 112 days from the start of therapy. For induction therapy outcomes, an apparent difference was that, in the two arms that included GCSF, both Pr(death) and Pr(CR) were higher and Pr(resistant disease) was lower compared with the two non-GCSF arms. For the salvage therapy outcomes, although there did not appear to be any difference between HDAC and other treatments in terms of the probabilities of death following either resistant disease or progression after CR, both residual survival times in these cases were much longer for patients who received a non-HDAC regimen as salvage. However, these conclusions ignore the combined effect of (front-line, salvage) on OS, which cannot be determined either from the summaries in Tables 1 and 2 or from conventional analyses based only on patient baseline covariates and front-line therapy.

As shown by Fig. 1, all patients received induction, and a second decision to choose a salvage treatment was made if either $Z_1 = 1$, for salvage B_1 following resistant disease, or $Z_1 = 2$ and $Z_2 = 1$, for salvage B_2 following progressive disease after CR. Under strategy (A, B_1, B_2), a patient cannot receive both B_1 and B_2 since achieving CR and having disease resistant to induction are disjoint events, and patients who die during induction receive neither B_1 nor B_2. Thus, each strategy is inherently outcome adaptive. Denote the set of possible induction treatments by $\mathcal{A} = \{a_1, \ldots, a_k\}$, the possible salvage treatments for patients with resistant disease by $\mathcal{B}_1 = \{b_{1,1}, \ldots, b_{1,l_1}\}$ and the possible salvage treatments for patients with disease progression after CR by $\mathcal{B}_2 = \{b_{2,1}, \ldots, b_{2,l_2}\}$. In typical practice, the oncologist chooses each patient's induction regimen on the basis of diagnostic information, such as the cytogenetic abnormality characterizing the leukaemia, white blood cell count, platelet count, age and performance status. In contrast, the AML–MDS data set arose from a randomized trial of four induction treatments $\{a_1, a_2, a_3, a_4\}$ in the 2×2 factorial design described earlier, with $\Pr(A = a_j) = \frac{1}{4}$ for each $j = 1, 2, 3, 4$. The salvage treatments were not assigned by randomization but rather were chosen subjectively by each patient's attending physician. Denoting the interim data for a patient with resistant disease by $\mathcal{H}_R$ and the data for a patient with progressive disease after CR by

$\mathcal{H}_{C,P}$, the salvage treatment decisions are functions $B_1 : \mathcal{H}_R \to \mathcal{B}_1$ and $B_2 : \mathcal{H}_{C,P} \to \mathcal{B}_2$. Salvage treatment in the first case is given at time T^R, and in the second case at time $T^C + T^{CP}$. One may formulate d more generally as a two-stage regime (A, B) in which B is a function from the set of all possible interim data $\{\mathcal{H}_R \cup \mathcal{H}_{C,P}\}$ that would require salvage therapy $\mathcal{B} = \mathcal{B}_1 \cup \mathcal{B}_2$. We consider it more informative to distinguish between the two types of salvage treatment, B_1 and B_2, because they are given the following qualitatively different patient histories. A treatment in $\mathcal{B}_1$ is an attempt to save a patient whose induction therapy failed, whereas a treatment in $\mathcal{B}_2$ is an attempt to reinduce CR after it was achieved initially but the patient's disease later progressed.

Each of the following distributions varies with patients' covariates $\mathbf{X} = (X_1, \ldots, X_q)$. To reduce the notation, we suppress this dependence when no meaning is lost. For initial outcome $j \equiv D, R, C$, denote by $h^j(t|A)$ the instantaneous risk of j at time t. To accommodate right-censoring, we denote the time from the start of induction to last follow-up by T^0, the time to initial outcome j or right censoring by $U^j = T^j \wedge T^0$, and $\delta^j = I(U^j = T^j)$. Note that at most one of U^D, U^R or U^C may be observed for each patient. We also assume, from here onwards, that censoring is conditionally independent of the transition times given prior transition times and other covariates including prior treatment (for example, the probability of being censored after resistance is independent of the time from resistance to death given X and T^R). In this case, the likelihood contribution for the initial outcome is

$$\mathcal{L}_1 = \prod_{j \equiv D,R,C} f^j(T^0|A)^{I(Z_1=j)\delta^j} \bar{F}^j(T^0|A)^{1-\delta^j}, \tag{2}$$

where $f^j(t|A) = h^j(t|A) \exp\{-\int_0^t h^j(s|A)\,ds\}$, and $\bar{F}^j(t|A) = \exp\{-\int_0^t h^j(s|A)\,ds\}$. For patients with resistant disease, where $Z_1 = 1$ and T^R is observed, denote $U^{RD} = T^{RD} \wedge (T^0 - T^R)$ and $\delta^{RD} = I(T^{RD} = U^{RD})$. Thus,

$$U^{RD} = \begin{cases} T^{RD} & \text{if } T^R + T^{RD} < T^0, \\ T^0 - T^R & \text{if } T^R < T^0 < T^R + T^{RD}. \end{cases}$$

Denote the instantaneous risk of death at time t following resistance ($Z_1 = 1$), given the time to resistance T^R, by $h^{RD|R}(t|T^R, A, B_1)$ for patients receiving A as induction, becoming resistant to A and receiving B_1 as salvage. The likelihood contribution of such patients is

$$\mathcal{L}_{2,R} = f^{RD|R}(U^{RD}|T^R, A, B_1)^{\delta^{RD}}\, \bar{F}^{RD|R}(U^{RD}|T^R, A, B_1)^{1-\delta^{RD}}, \tag{3}$$

where

$$f^{RD|R}(t|T^R, A, B_1) = h^{RD|R}(t|T^R, A, B_1)\, \bar{F}^{RD|R}(t|T^R, A, B_1), \tag{4}$$

and

$$\bar{F}^{RD|R}(t|T^R, A, B_1) = \exp\left\{-\int_0^t h^{RD|R}(s|T^R, A, B_1)\,ds\right\}. \tag{5}$$

Similarly, for patients achieving CR, so that $Z_1 = 2$ and T^C is observed, define $U^{CD} = T^{CD} \wedge (T^0 - T^C)$, $\delta^{CD} = I(T^{CD} = U^{CD})$, if there is no progression in disease (death or censoring occurs after remission), and $U^{CP} = T^{CP} \wedge (T^0 - T^C)$, and $\delta^{CP} = I(T^{CP} = U^{CP})$, if death does not occur before disease progression or censoring. Denote the instantaneous risk of death following remission for patients receiving induction treatment A at time t before disease progression by $h^{CD|C}(t|T^C, A)$. Similarly, define $h^{CP|C}(t|T^C, A)$ as the instantaneous risk of progression before death following remission at time t, given T^C and A. For patients who suffer progressive disease after CR, so that $\mathbf{Z} = (2, 1)$, define $T^{PD,0} = T^{PD} \wedge \{T^0 - (T^C + T^{CP})\}$ and $\delta^{PD} = I(T^{CD} = U^{CD})$.

Denote the conditional instantaneous risk of death following progression at time t for patients who achieve CR at time T^{C} with front-line A, then suffer progressive disease at time $T^{\mathrm{C}} + T^{\mathrm{CP}}$ and are given salvage B_2 by $h^{\mathrm{PD|CP}}(t|T^{\mathrm{C}}, T^{\mathrm{CP}}, A, B_2)$.

The contribution to the likelihood from a patient who achieves remission is therefore

$$\begin{aligned}\mathcal{L}_{2,C} = &\left\{ f^{\mathrm{CD|C}}(U^{\mathrm{CD}}|T^{\mathrm{C}}, A)^{\delta^{\mathrm{CD}}} \right\}^{I(Z_2=0)} \left\{ f^{\mathrm{CP|C}}(U^{\mathrm{CP}}|T^{\mathrm{C}}, A)^{\delta^{\mathrm{CP}}} \right\}^{I(Z_2=1)} \\ &\times \left\{ \bar{F}^{\mathrm{CD|C}}(U^{\mathrm{CD}}|T^{\mathrm{C}}, A) \bar{F}^{\mathrm{CP|C}}(U^{\mathrm{CP}}|T^{\mathrm{C}}, A) \right\}^{1-\delta^{\mathrm{CD}}-\delta^{\mathrm{CP}}} \\ &\times \left\{ f^{\mathrm{PD|CP}}(T^{\mathrm{PD},0}|T^{\mathrm{C}}, T^{\mathrm{CP}}, A, B_2)^{\delta^{\mathrm{PD}}} \right\} \\ &\times \left\{ \bar{F}^{\mathrm{PD|CP}}(T^{\mathrm{PD},0}|T^{\mathrm{C}}, T^{\mathrm{CP}}, A, B_2)^{1-\delta^{\mathrm{PD}}} \right\}^{I(Z_2=1)}, \end{aligned} \tag{6}$$

where each pair $f^j(\cdot|\cdot)$ and $\bar{F}^j(\cdot|\cdot)$ are defined on the basis of $h^j(\cdot|\cdot)$ similarly to the definitions that are given in the equations (4) and (5).

Combining expressions (2), (3) and (6), the overall likelihood is

$$\mathcal{L} = \mathcal{L}_1 \mathcal{L}_{2,\mathrm{R}}^{I\{Z_1=1\}} \mathcal{L}_{2,\mathrm{C}}^{I\{Z_1=2\}}. \tag{7}$$

3. Parametric models

For each of the seven transition times T^{D}, T^{R}, T^{RD}, T^{C}, T^{CD}, T^{CP} and T^{PD}, we used parametric regression models to account for effects of the baseline covariates and the treatment or treatments received before the noted event. For example, to model T^{D} when $Z_1 = 0$, the time to death during induction therapy, we fit members of the class of accelerated failure time regression models given by

$$\ln(T_i^{\mathrm{D}}) = \mathbf{X}_i \beta^{\mathrm{D}} + \sigma^{\mathrm{D}} \varepsilon_i, \qquad \text{for } i = 1, \ldots, n.$$

To obtain a good fit to the data we assumed, in turn, that ε_i followed an extreme value, standard extreme value (with fixed scale), logistic or normal distribution. These give respectively Weibull, exponential, log-logistic or log-normal distributions for T^{D}. The logarithm of any transition time observed before the transition time variable being modelled was included in $\mathbf{X}$ along with the baseline covariates. Specifically, the model for $[T^{\mathrm{RD}}|T^{\mathrm{R}}]$ included $\log(T^{\mathrm{R}})$, for $[T^{\mathrm{CP}}|T^{\mathrm{C}}]$ included $\log(T^{\mathrm{C}})$, for $[T^{\mathrm{CD}}|T^{\mathrm{C}}]$ included $\log(T^{\mathrm{C}})$ and for $[T^{\mathrm{PD}}|T^{\mathrm{C}}, T^{\mathrm{CP}}]$ included $\log(T^{\mathrm{C}})$ and $\log(T^{\mathrm{CP}})$ as covariates. For each of the seven transition times, we compared the fits of the four accelerated failure time regression models in terms of their Bayes information criterion (BIC) (Schwarz, 1978) values, and we used these to choose the best model. We compared the various treatment strategies by combining the fitted regression models to estimate the mean OS time for the distribution of $[T|A, B_1, B_2]$.

4. Evaluating treatment policies

The departure of our analyses from conventional evaluation of the effects of the induction treatments on OS or progression-free survival time begins with recognition of the facts that patients whose disease was resistant to induction, $Z_1 = 1$, or whose disease progressed after CR, $\mathbf{Z} = (2, 1)$, received salvage therapy. Our primary goal is to estimate and compare the effects of the strategies (A, B_1, B_2) on the OS time while also accounting for baseline covariate effects. We shall address this in two ways: one model based and the other utilizing IPTW estimating equations. Let $\theta(A, B_1, B_2)$ denote the summary parameter for the regime (A, B_1, B_2). For example, $\theta(A, B_1, B_2)$ could be $P(T > t^*|A, B_1, B_2)$, the survival probability beyond a particular time t^*

that is clinically meaningful, or $E(T|A, B_1, B_2)$, the mean OS time under regime (A, B_1, B_2). In our analyses, we use the latter. The mean OS can be expressed in terms of the parameters of counterfactual survival times, as follows:

$$\begin{aligned}\theta(A, B_1, B_2) = \int \Big\{ & \Pr(Z_1 = 0|A, X)\,\theta^{\mathrm{D}}(A, X) + \Pr(Z_1 = 1|A, X) \Big\{ \theta^{\mathrm{R}}(A, X) \\ & + \int \theta^{\mathrm{RD}}(A, B_1, X, X^{(\mathrm{R})})\, \mathrm{d}\mu(X^{(\mathrm{R})}) \Big\} \\ & + \Pr(Z_1 = 2|A, X) \Big(\theta^{\mathrm{C}}(A, X) + \int \Big[\Pr(Z_2 = 0|Z_1 = 2, A, X, X^{(\mathrm{C})}) \\ & \times \theta^{\mathrm{CD}}(A, X, X^{(\mathrm{C})}) + \Pr(Z_2 = 1|Z_1 = 2, A, X, X^{(\mathrm{C})}) \Big\{ \theta^{\mathrm{CP}}(A, X, X^{(\mathrm{C})}) \\ & + \int \theta^{\mathrm{PD}}(A, B_2, X, X^{(\mathrm{C})}, X^{(\mathrm{P})})\, \mathrm{d}\mu(X^{(\mathrm{P})}) \Big\} \Big]\, \mathrm{d}\mu(X^{(\mathrm{C})}) \Big) \Big\}\, \mathrm{d}\mu(X), \end{aligned} \tag{8}$$

where X represents the baseline covariates, $X^{(\mathrm{R})}$ denotes post-baseline covariates observed at or before treatment resistance, including $\log(T^{\mathrm{R}})$, $X^{(\mathrm{C})}$ denotes post-baseline covariates observed at or before observing CR, including $\log(T^{\mathrm{C}})$, and $X^{(\mathrm{P})}$ denotes the post-remission covariates observed at or before disease progression, including $\log(T^{\mathrm{P}})$. For $j \equiv \mathrm{D}, \mathrm{R}, \mathrm{RD}, \mathrm{C}, \mathrm{CP}, \mathrm{CD}, \mathrm{PD}$, $\theta^j(\cdot)$ is the conditional expectation of T^j given the arguments and other necessary conditions for the existence of T^j. For example, $\theta^{\mathrm{PD}}(A, B_2, X, X^{(\mathrm{C})}, X^{(\mathrm{P})}) = E[T^{\mathrm{PD}}|\mathbf{Z} = (2, 1), A, B_2, X, X^{(\mathrm{C})}, X^{(\mathrm{P})}]$. The measures $\mu(X)$ and $\mu(X^{(j)})$ are defined by the probability distribution of the covariates, and we estimate these by using the empirical measures. Equation (8) is an application of Robins's g-formula (Robins, 1986; Robins *et al.*, 2000) for estimating the effects of time varying treatment regimes.

Once the component models have been fitted, we substitute them into the expressions above to obtain the estimates for $\theta(A, B_1, B_2)$. In contrast with the likelihood-based equation (8), the IPTW estimates for strategy-specific overall mean survival is

$$\sum_{i=1}^{n} W_{AB_1B_2i} T_i \Big/ \sum_{i=1}^{n} W_{AB_1B_2i}, \tag{9}$$

where

$$\begin{aligned} W_{AB_1B_2i} = \frac{I_i(A)\delta_i}{\hat{K}(T_i)} & [I(Z_{1i} = 0) + I(Z_{1i} = 1)\, I_i(B_1)/\widehat{\Pr}(B_1|Z_{1i} = 1, A, X_i, X_i^{(\mathrm{R})}) \\ & + I(Z_{1i} = 2, Z_{2i} = 0) + I(Z_{1i} = 2, Z_{2i} = 1)\, I_i(B_2)/\widehat{\Pr}\{B_2|Z_i = (2, 1), A, X_i, X_i^{(\mathrm{C})}, X_i^{(\mathrm{P})}\}]. \end{aligned} \tag{10}$$

In equation (10), $\hat{K}(\cdot)$ is a consistent estimator of the censoring time survival distribution, δ_i is the indicator of whether death was observed for the ith patient, $I_i(E)$ is an indicator function taking the value 1 if the ith patient receives treatment E and the value 0 otherwise and $I(E_i)$ takes value 1 if the event E_i is true, and 0 otherwise. Under certain assumptions, such as consistency (the observed data equal the counterfactual data under consistent treatment assignment) and the sequential randomization assumption, which states that the probability of receiving treatment at a specific stage is independent of unobserved failure times given the covariates observed before treatment assignment, the above estimator has been shown to be consistent (Robins and Rotnitzky, 1992).

Secondary aims are to assess the effects of salvage treatments on the patient's remaining survival time, after resistant or progressive disease has been observed, as a function of past history. Specifically, we shall evaluate and compare the effects of B_1 on T^{RD} given A and T^{R}, and the effects of B_2 on T^{PD} given A, T^{C} and T^{CP}.

5. Analyses of the leukaemia data

It is well known that age and type of cytogenetic abnormality are highly reliable predictors of the probability of CR and OS time in AML or MDS. In particular, cytogenetic abnormality, characterized by missing portions of the fifth and seventh chromosomes (denoted by $(-5, -7)$), and older age both are strongly associated with a lower probability of CR and shorter OS. Because this trial's entry criteria required patients to have at least one unfavourable prognostic characteristic, the distributions of age and cytogenetic abnormality were different from those seen in the population of newly diagnosed AML–MDS patients. For example, only four patients had the comparatively favourable cytogenetic abnormality with an inversion of the 16th chromosome, or T(8,21), a translocation between chromosomes 8 and 21. Consequently, to take advantage of cytogenetic abnormality as a prognostic variable in our regression analyses, we grouped it into three categories: poor, $\{(-5, -7)\}$; intermediate, {diploid, $-Y$, or insufficient metaphases to classify}; good, $\{+8, 11Q, INV16, T(8, 21), MISC\}$. We used covariates for two different purposes:

(a) to model the transition times (e.g. the time to death, time between complete remission and death) in the likelihood-based method, and
(b) to model the probability of receiving each salvage treatment in the IPTW method (by using logistic regression). To realize the first objective, we fit accelerated failure time models for each of the seven failure times (T^{D}, T^{R}, T^{C}, T^{RD}, T^{CD}, T^{CP} and T^{PD}), assuming various parametric hazard models (exponential, Weibull, log-logistic and log-normal), as described in Section 3. For some of these event times the data were quite variable and included a small number of outliers that were extremely large compared with the other sample values. Consequently, to ensure stability of the model fits, six of the seven component models were fitted by restricting the time to the particular event to a fixed upper limit, with the limits set by first examining the observed distribution of each event time. Specifically, the variables T^{D}, T^{C}, T^{RD}, T^{CD}, T^{CP} and T^{PD} were restricted to 100, 110, 1408, 692, 1326 and 2274 days respectively. The BIC for the 28 model combinations are shown in Table 3. For each time component, the best model was chosen to be that minimizing the BIC among the four accelerated failure time distributions noted above. The best models were exponential for T^{RD} and T^{CD}, Weibull for T^{D}, log-logistic for T^{C} and T^{CP}, and log-normal for T^{R} and T^{PD} (Table 3), regardless of whether the outliers were included or excluded in the model fitting. We present details of the model fits without outliers.

5.1. Death during induction therapy

Unfortunately, many AML patients undergoing chemotherapy to induce CR die during this process, before either CR is achieved or it can be determined that the patient's disease is resistant to the induction chemotherapy. Although such deaths may be attributed to either the leukaemia or the chemotherapy, so-called 'regimen-related death', because both the disease and the treatment cause low white blood cell counts and other adverse events it often is very difficult to identify a sole cause of death. The patients in this study were especially susceptible to induction

Table 3. BIC for each of four different models fitted to each transition time in the leukaemia data set†

Transition	*BIC values for the following models:*			
	Exponential	*Weibull*	*Log-logistic*	*Log-normal*
Time to death (T^{D})	204.9	*197.4*	199.3	205.5
Time to resistance (T^{R})	108.7	65.9	63.1	*60.8*
Time to CR (T^{C})	247.5	131.3	*91.5*	92.6
Time to death from resistance (T^{RD})	*157.5*	161.4	166.5	171.8
Time to death from CR (T^{CD})	*28.0*	31.9	29.4	29.2
Time to disease progression from CR (T^{CP})	271.2	259.3	*248.4*	251.8
Time to death from disease progression (T^{PD})	288.9	297.0	284.9	*282.7*

†For each transition time, the minimum BIC is in italics.

Table 4. Maximum likelihood estimates from the accelerated failure time model for time to death, resistance and complete remission during the induction stage†

	Estimates for the following transitions and models:		
	Time to death, Weibull	*Time to resistance, log-normal*	*Time to CR, log-logistic*
Intercept	$_{2.80}3.79_{4.80}$	$_{3.67}4.36_{5.05}$	$_{3.10}3.38_{3.65}$
Front-line therapy			
FAI	$-_{0.15}0.29_{0.73}$	$-_{0.23}0.13_{0.50}$	$-_{0.13}0.05_{0.22}$
FAI + ATRA	$-_{0.40}0.08_{0.56}$	$-_{0.22}0.17_{0.57}$	$-_{0.21}-_{0.05}0.11$
FAI + GCSF	$-_{0.29}0.23_{0.60}$	$-_{0.42}0.09_{0.59}$	$-_{0.11}0.05_{0.22}$
FAI + GCSF + ATRA	Reference	—	—
Age (per year)	$-_{0.02}-0.005_{0.01}$	$-_{0.016}-0.007_{0.002}$	$-_{0.0015}0.0023_{0.006}$
Cytogenetic group‡			
0 *versus* 2	$-_{0.57}-0.13_{0.30}$	$-_{0.22}-0.11_{0.43}$	$-_{0.22}-0.08_{0.05}$
1 *versus* 2	$-_{0.57}-0.17_{0.24}$	$-_{0.13}0.04_{0.21}$	
σ	$_{0.54}0.65_{0.79}$	$_{0.30}0.38_{0.47}$	$_{0.15}0.17_{0.20}$

†Each parameter estimate is given with 95% confidence interval limits subscripted on the left and right.
‡0 = ('DIP,−Y','IM'); 1,'−5, −7'; 2, ('+8', '11Q', 'INV16', 'T(8,21)', 'MISC').

death due to their poor prognosis at entry to the trial, with overall rate of death during induction chemotherapy 33% (69/210), varying from 28% to 38% across the four induction regimens (p-value, 0.70; generalized Fisher exact test). In the fitted model for the three induction event times (Table 4), no baseline covariate was significantly associated with T^{D}. There did not appear to be any significant difference between the induction treatment effects on T^{D}, although ATRA may have had a slightly deleterious effect in that, among the 69 patients who died during induction, the patients in the two ATRA arms died a few days sooner, on average.

5.2. Resistance and death following resistance

Resistance to induction treatment occurred in 39 (18.6%) patients, relatively more frequently among patients receiving FAI and FAI plus ATRA (31% and 24% respectively) compared with those who received FAI plus GCSF or FAI plus ATRA plus GCSF (7.8% and 10% respectively).

Table 5. Maximum likelihood estimates from accelerated failure time models for residual time to death following disease being declared resistant to induction (T^{RD}), time to disease progression following complete remission (T^{CP}) and time to death from progression (T^{PD})†

	Estimates for the following times and models:		
	T^{RD}, *exponential*	T^{CP}, *log-logistic*	T^{PD}, *log-normal*
Intercept	$-6.31\ -1.32_{3.68}$	$6.49\ 8.11_{9.73}$	$-0.72\ 1.25_{3.23}$
Front-line therapy			
FAI *versus* FAI + GCSF + ATRA	$-0.57\ 0.64_{1.85}$	$-0.42\ 0.17_{0.76}$	$-0.86\ -0.21_{0.45}$
FAI + ATRA *versus* FAI + GCSF + ATRA	$0.55\ 1.83_{3.10}$	$-0.28\ 0.29_{0.86}$	$-0.09\ 0.50_{1.09}$
FAI + GCSF *versus* FAI + GCSF + ATRA	$0.87\ 2.83_{4.80}$	$0.03\ 0.62_{1.21}$	$-0.30\ 0.27_{0.84}$
Cytogenetic group‡			
0 *versus* 2	$-0.77\ 0.29_{1.36}$	$-0.34\ 0.03_{0.41}$	$-0.56\ -0.05_{0.45}$
1 *versus* 2	$-0.46\ 0.49_{1.44}$	$-0.95\ -0.52_{-0.10}$	$-0.90\ -0.32_{0.26}$
Age (per year)	$-0.05\ -0.01_{0.03}$	$-0.006\ -0.004_{0.014}$	$-0.04\ -0.03_{-0.01}$
log(time to resistance)	$0.11\ 1.20_{2.30}$	—	—
log(time to CR)	—	$-1.29\ -0.83_{-0.37}$	—
log(time to disease progression)	—	—	$0.55\ 0.85_{1.16}$
Salvage therapy HDAC (*versus* others)	$-4.07\ -1.61_{0.85}$	$-0.94\ -0.34_{0.27}$	$-0.84\ -0.39_{0.06}$
Interaction between induction and salvage therapy			
FAI × HDAC (*versus* others)	$-2.31\ 0.28_{2.88}$	$-0.13\ -0.80_{1.73}$	—
(FAI + ATRA) × HDAC (*versus* others)	$-0.99\ 1.66_{4.31}$	$-0.22\ 0.64_{1.51}$	—
(FAI + G) × HDAC (*versus* others)	$1.02\ 4.25_{7.48}$	$0.37\ 1.20_{2.03}$	—
Scale		$0.34\ 0.40_{0.49}$	$0.85\ 0.99_{1.15}$

†Each parameter estimate is given with 95% confidence interval limits subscripted on the left and right.
‡0 = ('DIP,−Y','IM'); 1,'−5, −7'; 2, ('+8', '11Q', 'INV16', 'T(8,21)', 'MISC').

The times to treatment resistance were similar across the four induction treatments, but with greater variability in the FAI plus GCSF arm (Table 4).

Among the 39 patients who were resistant to front-line treatment, 27 were given HDAC as salvage treatment. Two patients in this cohort were censored before observing death. Using likelihood ratio tests, factors that were associated with time from induction treatment resistance to death were age, $\log(T^R)$, front-line therapy, HDAC as salvage therapy (B_1) and their interaction (Table 5). Patients with older age, shorter T^R, front-line therapy FAI plus GCSF plus ATRA, or salvage therapy with HDAC died more quickly following their disease being declared resistant. Among patients given non-HDAC salvage therapy, T^{RD} was significantly greater if they received FAI plus ATRA or FAI plus GCSF compared with those who received FAI plus GCSF plus ATRA as the induction treatment. Also, for patients receiving FAI plus GCSF as induction treatment and HDAC as salvage therapy following treatment resistance, T^{RD} was significantly larger than those who received FAI plus GCSF but no HDAC or FAI plus GCSF plus ATRA either with or without HDAC salvage therapy.

5.3. Complete remission, progression and death after remission and progression

About half (48.6%) of the 210 patients achieved CR, with CR rates of 37%, 48%, 53% and 56% in the FAI, FAI plus ATRA, FAI plus GCSF and FAI plus GCSF plus ATRA arms respectively. The time to achieve CR did not differ significantly with front-line therapy (Table 4). Of the 102 patients who achieved CR, 93 (91%) had disease progression before death or being lost to follow-up. Among these, 53 (57%) received HDAC as salvage treatment. Since only nine patients died in CR, an intercept-only exponential accelerated failure time model was

used for modelling T^{CD}. In contrast, to model time between CR and progression (T^{CP}), a log-logistic model gave the best fit based on BIC values. Results for this fitted model are provided in Table 5.

Cytogenetics and T^{C} were associated with T^{CP}. The longer it took to achieve CR, the shorter the period of time that the patient remained in CR, which is a well known phenomenon in chemotherapy for AML or MDS (Shen and Thall, 1998; Estey *et al.*, 2000). Recall that cytogenetic abnormalities were classified as good ('+8', '11Q', 'INV16', 'T(8,21)', 'MISC'), intermediate (diploid, −Y or inevaluable) or poor (−5, −7). Patients with a 'good' cytogenetic abnormality were more likely to stay in CR longer than those in the intermediate or poor categories.

Residual time to death from disease progression after achieving CR was associated with age at entry, time to disease progression following CR and slightly with HDAC salvage therapy. Older patients were likely to have shorter residual life once disease progressed, compared with younger patients. Longer time to disease progression was associated with longer time between disease progression and death.

5.4. Strategy effects

Mean OS time estimates under each of the 16 different strategies in the leukaemia data were

Table 6. Strategy-specific estimates of mean OS time, based on the IPTW and likelihood-based methods†

Strategy (A, B_1, B_2)	*Estimated OS times (days) for the following estimators:*		
	IPTW	*Likelihood-based excluding outliers*	*Likelihood-based including outliers*
(FAI, HDAC, HDAC)	$_{149}189_{229}$	$_{220}281_{375}$	$_{242}335_{494}$
(FAI, HDAC, other)	$_{129}258_{397}$	$_{207}289_{432}$	$_{241}357_{541}$
(FAI, other, HDAC)	$_{162}214_{283}$	$_{261}346_{441}$	$_{281}400_{571}$
(FAI, other, other)	$_{147}275_{422}$	$_{248}354_{504}$	$_{280}422_{613}$
(FAI + ATRA, HDAC, HDAC)	$_{334}524_{751}$	$_{408}594_{864}$	$_{489}737_{1093}$
(FAI + ATRA, HDAC, other)	$_{263}460_{707}$	$_{376}507_{710}$	$_{469}655_{1009}$
(FAI + ATRA, other, HDAC)	$_{342}529_{749}$	$_{436}623_{922}$	$_{503}772_{1193}$
(FAI + ATRA, other, other)	$_{269}465_{713}$	$_{399}536_{763}$	$_{478}690_{1095}$
(FAI + GCSF, HDAC, HDAC)	$_{251}337_{445}$	$_{309}406_{1151}$	$_{353}493_{757}$
(FAI + GCSF, HDAC, other)	$_{217}307_{408}$	$_{345}457_{1217}$	$_{404}577_{850}$
(FAI + GCSF, other, HDAC)	$_{253}338_{445}$	$_{306}400_{1151}$	$_{355}486_{755}$
(FAI + GCSF, other, other)	$_{218}309_{410}$	$_{345}451_{1210}$	$_{402}569_{847}$
(FAI + GCSF + ATRA, HDAC, HDAC)	$_{169}328_{514}$	$_{246}343_{528}$	$_{282}413_{661}$
(FAI + GCSF + ATRA, HDAC, other)	$_{215}294_{367}$	$_{285}396_{563}$	$_{356}517_{824}$
(FAI + GCSF + ATRA, other, HDAC)	$_{187}351_{546}$	$_{281}381_{569}$	$_{320}451_{700}$
(FAI + GCSF + ATRA, other, other)	$_{236}318_{392}$	$_{324}434_{614}$	$_{395}554_{863}$

†Each estimate is given with 90% confidence interval limits subscripted on the left and right.

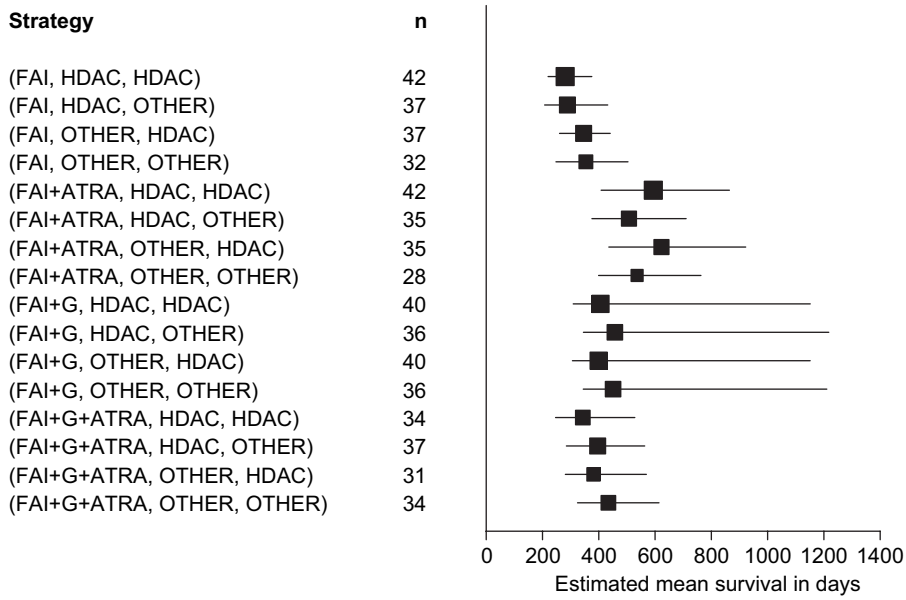

Fig. 2. Overall mean survival estimates and 90% non-parametric bootstrap confidence intervals for estimators under the likelihood method, excluding outliers: strategies such as (FAI, HDAC, HDAC) stand for 'give FAI as induction treatment, but if the patient's disease is resistant to therapy, or if relapse occurs after achieving CR, then give HDAC as salvage therapy'; for each strategy, the effective sample size n is the total number of patients in the study whose treatment regime was consistent with the strategy

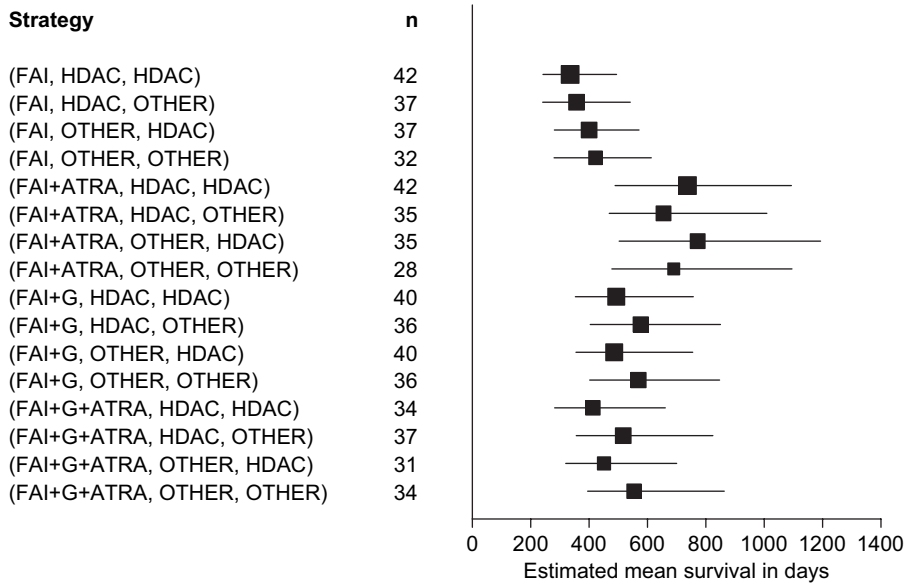

Fig. 3. Overall mean survival estimates and 90% non-parametric bootstrap confidence intervals for estimators under the likelihood method based on all observations in the data set including putative outliers: strategies such as (FAI, HDAC, HDAC) stand for 'give FAI as induction treatment, but if the patient's disease is resistant to therapy, or if relapse occurs after achieving CR, then give HDAC as salvage therapy'; for each strategy, the effective sample size n is the total number of patients in the study whose treatment regime was consistent with the strategy

calculated by using both the likelihood-based method and the IPTW method, from formulae (8) and (9) respectively. Confidence intervals for these estimates were calculated by using a non-parametric bootstrap method based on 500 with-replacement samples. The results are presented in Table 6. The likelihood-based bootstrap confidence intervals are illustrated in Fig. 2 by using the data with outliers removed, and in Fig. 3 by using the entire data set.

It is clear from Table 6 that the two methods give very different estimates for the mean OS time, with the likelihood-based estimator larger than the corresponding IPTW estimator for all strategies. The confidence intervals for the likelihood-based estimators were wider for 10 strategies and narrower for six strategies. These differences are not entirely surprising, since the two methods are very different. The likelihood-based method defines the OS time in terms of the seven transition times via equation(1), it uses regression models to account for effects of patient covariates and previous transition times, in addition to treatments, on each transition time and it marginalizes over the covariate distributions to obtain $\theta(A, B_1, B_2)$. Thus, the likelihood-based method estimates many covariate effects, which may be considered nuisance parameters. In contrast, the IPTW estimator ignores this structure and uses the covariates very differently, to estimate the strategy probability weights. Additionally, modelling each time-to-event variable separately reduces the effective sample size for each model fit and thus increases the overall variability of the strategy mean estimates, whereas the IPTW estimates are calculated from the overall sample, where time to death is the main source of random variation.

The substantive conclusions regarding the comparative effects of the 16 strategies are essentially the same for the two methods, however. Under both methods, the mean survival time estimates were smallest for the four strategies with FAI as front-line regardless of salvage treatment, with the exception that under the likelihood-based analysis the strategy (FAI + GCSF + ATRA, HDAC, HDAC) was slightly inferior to the strategies (FAI, other, HDAC) and (FAI, other, other), and the confidence intervals were smallest for these inferior strategies. As shown by Figs 2 and 3 for the likelihood-based approach, the mean overall survival estimates were largest for the four strategies with FAI plus ATRA as front-line treatment. With the likelihood-based approach, Figs 2 and 3 together show that the substantive conclusions were insensitive to whether the outliers were included or not, although using all the data gave much smaller bootstrap confidence intervals for the means that were associated with the four strategies (FAI + GCSF, B_1, B_2). Most importantly, all approaches showed that, among the four best strategies, (FAI + ATRA, B_1, HDAC) was superior to (FAI + ATRA, B_1, other) regardless of B_1. These results suggest that

(a) FAI plus ATRA was the best remission induction therapy,
(b) if the patient's disease was resistant to FAI plus ATRA as induction therapy then it was irrelevant whether the salvage therapy contained HDAC and
(c) if the patient achieved CR with FAI plus ATRA and later relapsed then salvage therapy with HDAC was superior.

These conclusions, although not confirmatory, are in sharp contrast with those given by Estey *et al.* (1999) based on conventional Cox regression model analyses and hypothesis testing, which were that none of the three adjuvant combinations FAI plus ATRA, FAI plus GCSF or FAI plus ATRA plus GCSF were significantly different from FAI alone with respect to either survival or event-free survival time, considering only the front-line therapies.

An exhaustive formal comparison of the 16 strategies based on our analyses would require 120 pairwise tests, which is an unavoidable multiple-comparisons problem that arises when evaluating multistage strategies. The trial was not designed to identify multistage strategies, and no clinical study can be powered to conduct so many pairwise tests reliably. With regard to estima-

tion of strategy-specific mean survival times, however, although the 90% confidence intervals in Table 6 have a large degree of overlap, in terms of the estimated means it is striking that the two strategies (FAI + ATRA, HDAC, HDAC) and (FAI + ATRA, other, HDAC) appear to be superior, with (FAI + ATRA, HDAC, other) and (FAI + ATRA, other, other) ranked third and fourth, on the basis of both of the two very different analytic approaches that we have taken here.

6. Discussion

We have reanalysed a data set from a four-arm clinical trial that was designed to assess the effects of adding ATRA, GCSF or both to FAI for treatment of newly diagnosed AML or high risk MDS. The purpose of our analysis has been to account for the multistage adaptive nature of the therapy that is actually received by the patients, which in particular included salvage therapies given if either the patient's disease was resistant to initial remission induction therapy or the patient relapsed after achieving a CR. This motivated evaluation of 16 possible two-stage strategies for choosing induction and salvage therapies. We employed two very different methods of analysis. The first was based on a detailed likelihood that accounted for all possible outcome paths, the transition times between successive states and effects of covariates on each transition time. The second method employed IPTW-based estimating equations and was much simpler, using covariates only to estimate the probabilities of the various strategies. Although the two methods gave numerically different estimates of OS time, they agreed with regard to the worst and best strategies. Perhaps the most important conclusion was that these analyses both identified two strategies that appeared to be superior, which is a conclusion that was not seen earlier when only front-line treatments were evaluated. The trial was motivated by the idea that retinoids, such as ATRA, might improve the outcome for AML or MDS patients when given with chemotherapy, since it was well established at the time that this trial was initiated that ATRA has substantive antidisease activity in treating acute promyelocytic leukaemia (Estey *et al.*, 1997). On the basis of our reanalyses of this data set, it seems that this idea for treatment of AML or MDS may have been correct. Although our results cannot be considered confirmatory, it seems that analyses of the types presented here, if they had been carried out in 1999, might have altered subsequent decisions of what combinations to study next, as well as showing the value of considering two-stage strategies. An open question that now seems important is whether the addition of ATRA to currently used front-line and salvage chemotherapy combinations for AML and MDS may improve the OS time. More generally, our analyses of this data set strongly suggest that a large amount of valuable information may be lost when using conventional methods based on initial treatment alone to analyse clinical trials.

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Appendix A: Proof of the *g*-formula in equation (8)

First note that the overall survival time T is a mixture of component transition times:

$$T = I(Z_1 = 0)T^{\mathrm{D}} + I(Z_1 = 1)(T^{\mathrm{R}} + T^{\mathrm{RD}}) + I(Z_1 = 2)\{I(Z_2 = 0)(T^{\mathrm{C}} + T^{\mathrm{CD}}) + I(Z_2 = 1)(T^{\mathrm{C}} + T^{\mathrm{CP}} + T^{\mathrm{PD}})\}$$

$$= I(Z_1 = 0)T^{\mathrm{D}} \tag{11}$$
$$+ I(Z_1 = 1)(T^{\mathrm{R}} + T^{\mathrm{RD}}) \tag{12}$$
$$+ I(Z_1 = 2)\{T^{\mathrm{C}} + I(Z_2 = 0)T^{\mathrm{CD}} + I(Z_2 = 1)(T^{\mathrm{CP}} + T^{\mathrm{PD}})\}. \tag{13}$$

Suppose first that there are no covariates. Then, to find the mean of T under a given treatment strategy (A, B_1, B_2), one would take the expectation of the components on the right-hand side of this equation under treatment assignment that is consistent with this strategy. Therefore,

$$\begin{aligned}\theta(A, B_1, B_2) &= E[T|(A, B_1, B_2)] \\ &= P(Z_1 = 0|A)\, E[T^{\mathrm{D}}|A, Z_1 = 0] \\ &\quad + P(Z_1 = 1|A)(E[T^{\mathrm{R}}|A, Z_1 = 1] + E[T^{\mathrm{RD}}|A, B_1, Z_1 = 1]) \\ &\quad + P(Z_1 = 2|A)\left\{E[T^{\mathrm{C}}|A, Z_1 = 2] + P(Z_2 = 0|Z_1 = 2, A)\, E[T^{\mathrm{CD}}|A, Z_1 = 2, Z_2 = 0]\right. \\ &\quad + P(Z_2 = 1|Z_1 = 2, A)(E[T^{\mathrm{CP}}|A, Z_1 = 2, Z_2 = 1] \\ &\quad \left. + E[T^{\mathrm{PD}}|A, B_2, Z_1 = 2, Z_2 = 1])\right\}. \end{aligned} \tag{14}$$

Now, using covariates to model the conditional probabilities and expectations on the right-hand side of this equation, and integrating over the respective covariate distributions, we obtain the g-formula in equation (8).

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