

Evaluating Joint Effects of Induction-Salvage Treatment Regimes on Overall Survival in Acute Leukemia

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SUMMARY. Typical oncology practice includes not only an initial, frontline treatment, but also one or more subsequent treatments given when the initial treatment has failed. The oncologist chooses a treatment at each stage based on the patient's baseline covariates and history of all previous treatments and outcomes. Such sequentially adaptive medical decision-making processes are known as dynamic treatment regimes, treatment policies, or multi-stage adaptive treatment strategies. Conventional analyses in terms of frontline treatments that ignore subsequent treatments may lead to very misleading conclusions regarding effects on overall survival time. We are motivated by data from a randomized trial of four combination chemotherapies given as frontline treatments to patients with acute leukemia. Most of the patients in the trial also received a second-line treatment, chosen adaptively and subjectively rather than by randomization, either because the initial treatment was ineffective or the patient's cancer was eradicated but later recurred. We evaluate the effects on overall survival

time of the 16 possible two-stage strategies that actually were used. Our methods include a likelihood-based regression approach in which the transition times of all possible multi-stage outcome paths are modeled, and the use of estimating equations with inverse probability of treatment weighting to correct for bias. Our results show that, while the two approaches give different numerical estimates of mean survival time, they lead to the same substantive conclusions when comparing the two-stage regimes.

KEY WORDS: Causal inference; Clinical trial; Dynamic treatment regime; Treatment policy

1 Introduction

Confirmatory evaluation of a new treatment for cancer often is based on a randomized clinical trial with overall survival (OS) time as the primary endpoint. Compared to intermediate outcomes that may be used because they are observed sooner, such as disease-free survival (DFS) time or tumor response, OS time is widely considered to be the “gold standard” for treatment evaluation because prolonging survival is the ultimate goal of cancer therapy. Comparative treatment effects on OS typically are defined as ratios or differences between hazard functions, means or medians, or as parameters in a regression model accounting for both treatment and patient covariate effects. A fundamental problem with this statistical paradigm is that, in typical oncology practice, a patient receives not only an initial, frontline treatment, but also one or more subsequent treatments, most often chosen adaptively by the physician based on the patient’s previous history of treatments and observed outcomes. Each patient’s OS time thus may depend on the entire sequence of treatments and the adaptive manner in which they were chosen, rather than only the frontline treatment. Consequently, a conventional statistical analysis of frontline treatment effects on OS that ignores subsequent

treatments may lead to very misleading conclusions.

This type of sequentially adaptive medical decision-making process is known variously as a dynamic treatment regime (DTR), treatment policy, or multi-stage adaptive treatment strategy. There is a substantial statistical literature on methods for analyzing observational or clinical trial data having this structure (Robins, 1986; Robins and Rotnitzky, 1992; Murphy, van der Laan and Robins, 2001; Lunceford, Davidian and Tsiatis, 2002; Murphy, 2003; Wahed and Tsiatis, 2004, 2006). There also has been a growing literature on methods for the design and conduct of clinical trials to evaluate and compare DTRs (Lavori and Dawson, 2000, 2004; Thall, Millikan and Sung, 2000; Thall, Sung and Estey, 2002; Murphy, 2005; Zhao, Kosorok and Zeng, 2009).

The particular 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 frontline treatment has failed. In such cases, it is common clinical practice to choose and administer a second line, “salvage” treatment, which typically is different from the patient’s frontline treatment. The data set that we will analyze arose from a randomized trial of four combination chemotherapies given as frontline treatments to patients with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS), which are myeloid hematologic malignancies, i.e., blood cancers that originate in the bone marrow. Since the trial’s entry criteria required each patient to have at least one of several characteristics predictive of poor prognosis, the diseases were rapidly fatal and thus required very aggressive treatment for the patient to have any hope of long term survival. In therapeutic practice, patients with advanced AML or MDS often are treated the same way, and this was the case in the trial considered here. Aside from the particular disease subtype, AML/MDS is easy to diagnose, since it is characterized by an unusually large percentage of

blood cell blasts, also called stem cells, which are mostly leukemia cells that remain in an undifferentiated state. Consequently, the patient has a deficit of normal mature, functional blood cells, such as red cells, T-cells, and white blood cells (WBCs).

Chemotherapy of AML/MDS proceeds in stages. The aim is to kill cancer cells and bring the patient's blasts, platelets and WBCs back to normal functional levels. At the start, a "remission induction" (frontline) chemotherapy is given, with the immediate aim to achieve a complete remission (CR), defined as the patient having $< 5\%$ blast cells, a platelet count $> 10^5/\text{mm}^3$ and WBC count $> 10^3/\text{mm}^3$, based on a bone marrow biopsy. Achieving CR is a necessary condition for long term survival in AML/MDS patients, but it does not guarantee long-term survival because a patient whose chemotherapy achieves CR still may relapse subsequently, that is, the disease may later re-appear. Relapse may be due to the fact that the induction chemotherapy failed to eradicate the disease, possibly because the most chemotherapy-resistant cancer cells among several subtypes survive and later multiply. Identifying reasons for chemotherapy resistance is an area of intense research activity in virtually all types of cancer. In chemotherapy of AML/MDS, if the induction treatment does not achieve a CR, or if a CR is achieved but the patient suffers a relapse, then a salvage treatment usually is given in a second attempt to achieve a CR. Salvage therapy may consist of another chemotherapy, usually different from that given as induction or, in some cases, a stem cell transplant.

The AML/MDS trial considered here used a 2×2 randomized factorial design with the baseline chemotherapy combination consisting of fludarabine + cytosine arabinoside ("ara-C") + idarubicin (FAI). The four combinations studied were FAI, FAI + all-trans retinoic acid (ATRA, an acid form of vitamin A), FAI + granulocyte colony stimulating factor (G-CSF) and FAI + ATRA + G-CSF. The primary scientific aim of the trial was to assess the

effects of adding ATRA, G-CSF, or both to FAI on the probability of success, defined as the patient being alive and in CR six months after the start of treatment. Analyses of this data set using conventional methods have been reported previously (Estey, Thall, Pierce et al., 1999), including logistic regression to assess the effects of the treatments and patient baseline covariates on the probability of achieving CR, Kaplan-Meier estimates of OS for the four treatment groups, and Cox model regression to assess joint treatment and covariate effects on OS time. These analyses, like nearly all statistical analyses of similar data sets reported in the medical literature, were based on the simplifying assumption that the only relevant treatments were those given initially, as frontline therapy.

Consideration of both frontline 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 Figure 1. While the figure was constructed specifically for AML/MDS, the possible pathways of therapies and outcomes for many other diseases are qualitatively very similar. Figure 1 shows that a patient undergoing this type of chemotherapeutic treatment regime may die (i) during induction therapy, (ii) following salvage therapy given if the disease is resistant to induction, (iii) while in CR, or (iv) following disease progression after CR. The putative reasons for each of these different types of death are complex, and it often is difficult to assign a cause of death. For example, while it may not appear to make sense that a patient might die while in CR, the cumulative damage to the patient's immune system and internal organs from both the chemotherapy and the disease may prove fatal even though CR has been achieved. This problem, and the fact that chemotherapy is rarely curative, have motivated extensive research to identify so-called "targeted therapies." These are molecular or biologic agents that, in principle, are tailored to selectively identify and kill leukemia cells, or that aim to

protect the patient’s normal cells from the adverse effects of chemotherapy.

In our data analyses, our primary goal is to evaluate the combined effects of induction and salvage combinations on OS time. In order to assess the effects of salvage treatments on subsequent survival time, we will keep track of the various transition times between states, as shown in Figure 1. The possible treatment regimes can be characterized 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 therapy, and B_2 denotes salvage therapy for patients with disease progression following a CR achieved with induction therapy. For a given regime (A, B_1, B_2) , each patient received A only, (A, B_1) , or (A, B_2) . We will discuss this point further in Section 2. Our main motivation for focusing on entire regimes rather than on individual treatments is that the optimal regime $d^{opt} = (A, B_1, B_2)^{opt}$ may not correspond to what would be obtained by optimizing A , B_1 , and B_2 separately for each stage of therapy. A common example in chemotherapy for AML/MDS is that a very aggressive frontline treatment may maximize $\Pr(\text{CR})$, but it also may cause so much damage to the patient’s immune system that a subsequent rapid relapse is likely and, moreover, any salvage therapy B_2 given following relapse is unlikely to achieve a second CR. As a toy numerical illustration, suppose that two induction regimens, $A^{(1)}$ and $A^{(2)}$, both provide a mean OS of 12 months if CR is achieved, with $\Pr(\text{CR} | A^{(1)}) = 0.60$ and $\Pr(\text{CR} | A^{(2)}) = 0.40$, and both have induction death probabilities of 0.10. While this might seem to indicate that $A^{(1)}$ is greatly superior to $A^{(2)}$, suppose that $A^{(1)}$ is much more immunosuppressive and consequently, for simplicity, any salvage regimen B_1 given following resistance to $A^{(1)}$ yields a mean OS of 2 months compared to 12 months with salvage following resistance to $A^{(2)}$. The mean OS for the two regimens are then $0.6 \times 12 + 0.3 \times 2 = 7.8$ months for $A^{(1)}$ compared to $0.4 \times 12 + 0.5 \times 12 = 10.8$ months for $A^{(2)}$. This sort of phenomenon occurs in many areas of oncology. A different type of multi-

stage regime effect, also potentially quite important, is that in which there is either a beneficial or harmful synergistic effect of two particular treatments given in sequence. For example, suppose that a particular chemotherapy is only moderately successful as first line therapy to de-bulk a solid tumor, but it gives a high probability that the remaining tumor will be resectable, and when surgical resection is performed the two treatments together maximize OS. That is, a particular first line treatment may be only moderately successful in terms of immediate effect but best at facilitating what is given next. These considerations may have profound implications for clinical practice, since a physician giving A^{opt} determined by considering only frontline treatment effects may unknowingly be setting patients on pathways that include only greatly inferior regimes.

In the data set considered here, another major issue is that, while patients were randomized among the four induction combinations to choose A , the salvage treatments B_1 and B_2 were not assigned by randomization, but rather were chosen by the attending physician on a patient-by-patient basis. Consequently, considering the multi-course structure of the patients' actual therapy, the data are actually observational because salvage treatments were not chosen by randomization. This motivates our use of inverse probability of treatment weighting (IPTW) in our estimation methods. IPTW estimators (Robins, Hernan and Brumback, 2000) account for the variation in receiving a specific treatment by weighting each observation by the inverse of the propensity 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

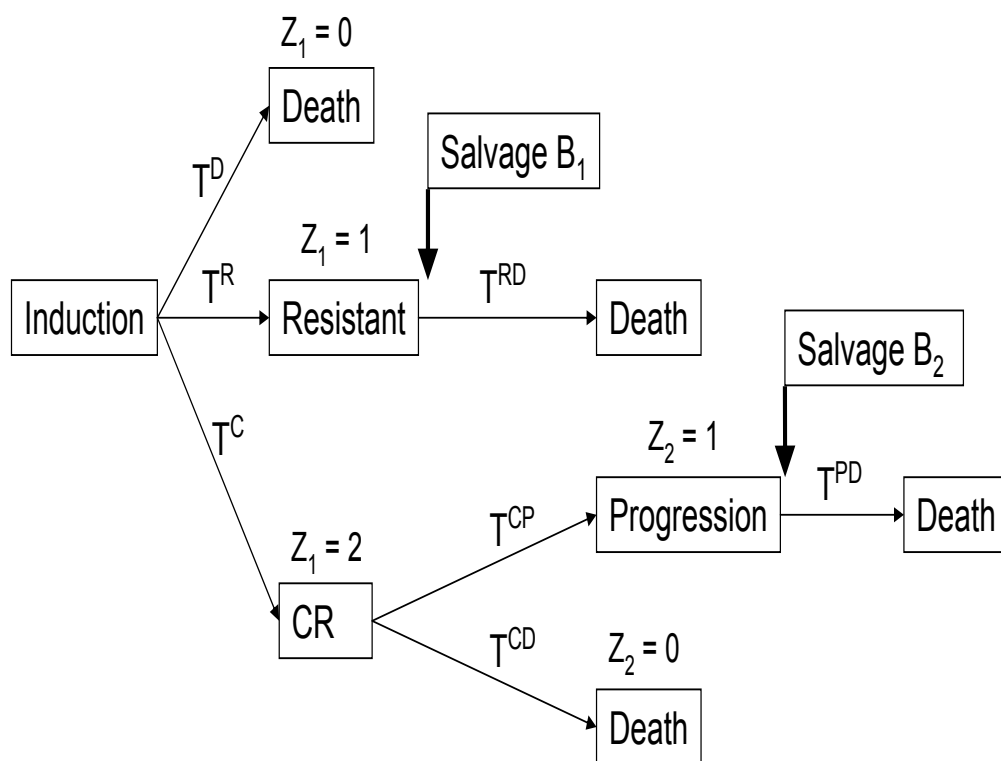
analyses that ignore salvage therapy. We close with a brief discussion in Section 5.

2 Data Structure and Likelihoods

To provide a framework for analysis of the treatment regimes actually used in the AML/MDS trial, we first establish notation for the transition times and their likelihood functions. As shown by Figure 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 , and use the categorical variable Z_1 to keep track of which event occurred. Denoting the minimum of a and b by $a \wedge b$, we define $Z_1 = 0$ if $T^D < T^R \wedge T^C$, $Z_1 = 1$ if $T^R < T^D \wedge T^C$ and $Z_1 = 2$ if $T^C < T^D \wedge T^R$. The transition time from the patient’s disease being declared resistant to death is denoted by T^{RD} . 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 $Z_2 = I(T^{CP} < T^{CD})$ 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 $Z_1 = 1$. Similarly, T^{CP} , T^{CD} and Z_2 are defined only if $Z_1 = 2$, and T^{PD} is defined only if $Z_2 = 1$.

Aside from discontinuation of therapy due to a reason other than death, including administrative right censoring or drop-out, each patient’s observed sequence of transition times consisted of exactly one of the four vectors (T^D) , (T^R, T^{RD}) , (T^C, T^{CP}, T^{PD}) , or (T^C, T^{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

Figure 1: Possible pathways of successive states, transition times and salvage therapy following induction treatment in acute leukemia patients.



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:

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

Table 1 summarizes the counts and median transition times for the seven possible events illustrated in Figure 1 for the leukemia data. These include the three induction therapy outcomes (indexed by Z_1) for each treatment arm, and the four possible subsequent outcomes. Due to the fact that there were many different salvage treatments, these were classified as either containing high dose ara-C (HDAC) or not. The small discrepancy between 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 covariate effects, it shows the generally poor outcomes in that only 48% of patients achieved a CR while 33% died during induction therapy, with this type of death very likely to occur in less than two 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. In terms of induction therapy outcomes, an apparent difference was that, in the two arms that included G-CSF, both $\text{Pr}(\text{Death})$ and $\text{Pr}(\text{CR})$ were higher and $\text{Pr}(\text{Resistant Disease})$ was lower compared to the two non-G-CSF arms. For the salvage therapy outcomes, while 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 of the residual survival times in these cases were much longer for patients who received a

Table 1: Summary of outcomes following induction and salvage therapy, overall and by frontline treatment. The sample median of each transition time is given in days, with lower and upper 95% confidence interval limits subscripted on the left and right.

Group	Initial Outcomes Following Induction Therapy						Total N
	Death		Resistant Disease		CR		
	N (%)	T^D	N (%)	T^R	N (%)	T^C	
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+G	20 (38)	$_{22}32_{45}$	4 (8)	$_{27}77_{112}$	28 (54)	$_{29}36_{40}$	52
FAI+G+ATRA	17 (34)	$_{14}21_{30}$	5 (10)	$_{48}51_{70}$	28 (56)	$_{28}32_{38}$	50

Group	Outcomes Following CR or Resistant Disease							
	Death After Res		Death in CR		Prog After CR		Death After Prog	
	N (%)	T^{RD}	N (%)	T^{CD}	N (%)	T^{CP}	N (%)	T^{PD}
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 Trt	12 (100)	$_{82}130_{252}$	–	–	–	–	36 (90)	$_{122}158_{191}$

non-HDAC regimen as salvage. These conclusions ignore the combined effect of frontline and salvage therapy on OS, however, which cannot be determined either from the summaries in Table 1 or from conventional analyses based only on patient baseline covariates and frontline therapy.

As shown by Figure 1, while all patients received induction, a second treatment decision consisting of the choice of salvage treatment was made if either $Z_1 = 1$, motivating salvage B_1 following resistant disease, or $Z_1 = 2$ and $Z_2 = 1$, motivating salvage B_2 following progressive disease after CR. Note that, 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, while patients who die during induction receive neither B_1 nor B_2 . In this way, each strategy is inherently outcome-adaptive. Denote the set of possible induction treatments by $\mathcal{A} = \{a_1, \dots, a_k\}$, the possible salvage treatments given to patients with resistant disease by $\mathcal{B}_1 = \{b_{1,1}, \dots, b_{1,l_1}\}$, and the possible salvage treatments given to patients with disease progression after CR by $\mathcal{B}_2 = \{b_{2,1}, \dots, b_{2,l_2}\}$. In typical clinical practice, A is a function from the set of possible baseline covariates to \mathcal{A} , because the oncologist chooses each patient's induction regimen based on diagnostic information such as the type of cytogenetic abnormality characterizing the leukemic cells, WBC count, platelet count, age and performance status. In contrast, the AML/MDS data considered here arose from a randomized trial in which all four induction treatments $\{a_1, a_2, a_3, a_4\}$ in the 2×2 factorial design described earlier were considered appropriate for patients meeting the trial's entry criteria, with $\Pr(A = a_j) = \frac{1}{4}$ for each $j = 1, 2, 3, 4$. As is typically the case in leukemia therapeutics and most other cancers, 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 $B_1 : \mathcal{H}_R \rightarrow \mathcal{B}_1$ and $B_2 : \mathcal{H}_{C,P} \rightarrow \mathcal{B}_2$, bearing in mind that the 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 administered following patient histories that differ qualitatively in a very important way. 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 re-induce CR after it was achieved initially but the patient's disease later progressed.

Since each of the following distributions varies with patient covariates, $\mathbf{X} = (X_1, \dots, X_q)$, to reduce notation we will suppress this dependence when no meaning is lost. For initial outcome $j = D, R$, or C , denote the probability density function (pdf), cumulative distribution function (cdf) and survivor function (sf) of T^j for a patient treated with frontline induction treatment A by $f^j(t | A)$, $F^j(t | A)$ and $\bar{F}^j(t | A) = 1 - F^j(t | A)$, respectively. To accommodate right-censoring, we denote the time from start of induction to last follow up by T^0 , the time to initial outcome $j = D, R$ or C or right-censoring by $U^j = T^j \wedge T^0$ and we denote $\delta^j = I(U^j = T^j)$. Note that at most one of U^D, U^R or U^C may be observed for each patient. The contribution to the likelihood for the initial outcome is

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

For patients with resistant disease, where $Z_1 = 1$ and T^R is observed, denote $U^{RD} = T^{RD} \wedge (T^0 - T^R)$. Thus,

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

and we define $\delta^{RD} = I(T^{RD} = U^{RD})$. Denoting the conditional pdf of $[T^{RD} | T^R]$ for patients with resistant disease given frontline A and salvage B_1 by $f^{RD|R}(t | T^R, A, B_1)$, for $Z_1 = 1$, conditional on T^R the second likelihood contribution of these patients is

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

Similarly, for patients achieving CR, so that $Z_1 = 2$ and T^C is observed, denote $U^{CD} = T^{CD} \wedge (T^0 - T^C)$, define $\delta^{CD} = I(T^{CD} = U^{CD})$, and denote the conditional pdf of $[T^{CD} | T^C]$ for patients achieving CR with frontline therapy A by $f^{CD|C}(t | T^C, A)$. Given T^C , for $\mathbf{Z} = (2,0)$, the second likelihood contribution of patients who die in CR ($Z_2 = 0$) is

$$\mathcal{L}_{2,CD} = \{f^{CD|C}(U^{CD} | T^C, A)\}^{\delta^{CD}} \{\bar{F}^{CD|R}(U^{CD} | T^R, A)\}^{1-\delta^{CD}} \quad (4)$$

Finally, 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 pdf of the time from progression to death, $[T^{PD} | T^C, T^{CP}]$, for patients who achieve CR with frontline A , then suffer progressive disease and are given salvage B_2 by $f^{PD|CP}(t | T^C, T^{CP}, A, B_2)$. For $\mathbf{Z} = (2,1)$, the second likelihood contribution of these patients is

$$\mathcal{L}_{2,PD} = \{f^{PD|CP}(T^{PD,0} | T^C, T^{CP}, A, B_2)\}^{\delta^{PD}} \{\bar{F}^{PD|CP}(T^{PD,0} | T^C, T^{CP}, A, B_2)\}^{1-\delta^{PD}} \quad (5)$$

Combining expressions (2) – (5), the likelihood contribution of a patient treated with regime (A, B_1, B_2) is

$$\mathcal{L} = \mathcal{L}_1 \times \{\mathcal{L}_{2,RD}\}^{I\{Z_1=1\}} \times \{\mathcal{L}_{2,CD}\}^{I\{\mathbf{Z}=(2,0)\}} \times \{\mathcal{L}_{2,PD}\}^{I\{\mathbf{Z}=(2,1)\}} \quad (6)$$

3 Parametric Models

For each of the seven transition time variables, 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 prior to 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 (AFT) regression models given by

$$\ln T_i^D = \mathbf{X}_i \beta^D + \sigma^D \epsilon_i, \quad \text{for } i = 1, \dots, n.$$

To obtain a good fit to the data, we assumed, in turn, that the unobservable random variable 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 . For each model fit, the log of any transition time observed prior to the transition time variable being modeled was included in \mathbf{X} along with the baseline covariates. Specifically, the model for $[T^{RD} | T^R]$ included $\log(T^R)$, for $[T^{CP} | T^C]$ included $\log(T^C)$, for $[T^{CD} | T^C]$ included $\log(T^C)$, and for $[T^{PD} | T^C, T^{CP}]$ included $\log(T^C)$ and $\log(T^{CP})$ as covariates. For each of the seven transition times, we compared the fits of the four AFT regression models in terms of their Bayes information criterion (BIC, Schwarz, 1978) values, and we used this to choose a best model. We compared the different treatment strategies by combining the fitted regression models to estimate 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 OS time while also accounting for baseline covariate

effects. We will address this in two ways, one model-based and the other utilizing 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 data analyses, we use the latter. Mean OS can be expressed in terms of the parameters of counterfactual survival times, as follows:

$$\begin{aligned}
\theta(A, B_1, B_2) &= \int \left\{ Pr(Z_1 = 0 | A, X) \theta^D(A, X) + Pr(Z_1 = 1 | A, X) \left[\theta^R(A, X) \right. \right. \\
&\quad \left. \left. + \int \theta^{RD}(A, B_1, X, X^{(R)}) d\mu(X^{(R)}) \right] \right. \\
&\quad \left. + Pr(Z_1 = 2 | A, X) \left\{ \theta^C(A, X) + \int \left[Pr(Z_2 = 0 | Z_1 = 2, A, X, X^{(C)}) \right. \right. \right. \\
&\quad \quad \left. \left. \times \theta^{CD}(A, X, X^{(C)}) + Pr(Z_2 = 1 | Z_1 = 2, A, X, X^{(C)}) \left(\theta^{CP}(A, X, X^{(C)}) \right) \right. \right. \\
&\quad \left. \left. \left. + \int \theta^{PD}(A, B_2, X, X^{(C)}, X^{(P)}) d\mu(X^{(P)}) \right] d\mu(X^{(C)}) \right\} \right\} d\mu(X), \quad (7)
\end{aligned}$$

where X represents the baseline covariates, $X^{(R)}$ denotes the post baseline covariates observed at or before treatment resistance, including log time to treatment resistance, $X^{(C)}$ denotes the post baseline covariates observed at or before observing CR, including log time to treatment remission, and $X^{(P)}$ denotes the post-remission covariates observed at or before disease progression, including log time to disease progression. For $j \in \{D, R, RD, C, CP, CD, PD\}$, $\theta^j(\cdot)$ is the conditional expectation of T^j given the arguments. The measures $\mu(X)$ and $\mu(X^{(j)})$ are defined by the probability distribution of the covariates, and we estimate these using the empirical measures.

Once the component models are estimated as described previously, we can substitute them into the expressions above to obtain the estimates for $\theta(A, B_1, B_2)$. In contrast with the likelihood-based equation (7), the IPTW estimates for strategy-specific overall mean

survival is

$$\frac{\sum_{i=1}^n W_{AB_1B_2i} T_i}{\sum_{i=1}^n W_{AB_1B_2i}}, \quad (8)$$

where

$$W_{AB_1B_2i} = \frac{I_i(A)\delta_i}{\hat{K}(T_i)} \left\{ I(Z_{1i} = 0) + I(Z_{1i} = 1)I_i(B_1)/\hat{P}r(B_1|Z_{1i} = 1, A, X_i, X_i^{(R)}) + \right. \\ \left. I(Z_{1i} = 2, Z_{2i} = 0) + I(Z_{1i} = 2, Z_{2i} = 1)I_i(B_2)/\hat{P}r(B_2|Z_i = (2, 1), A, X_i, X_i^{(C)}, X_i^{(P)}) \right\}. \quad (9)$$

In equation (9), $\hat{K}(\cdot)$ is a consistent estimator of the censoring time survival distribution, δ_i is the indicator of whether death was observed for the i th patient, $I_i(E)$ is an indicator function taking the value 1 if i th 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. Secondary aims are to assess the effects of salvage treatments on the patient's remaining survival time, after resistant or progressive disease is observed, as a function of past history. Specifically, we will 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 Leukemia 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/MDS. In particular, the cytogenetic abnormality (-5,-7), characterized by missing portions of the 5th and 7th chromosomes, and older age both are strongly associated with a lower probability of CR and shorter OS in AML/MDS. Because this trial's entry criteria required the patient to have at least one unfavorable prognostic characteristic, however, the distributions of age and cytogenetic categories were different from those seen in the population of all newly diagnosed AML/MDS patients. E.g., only 4 patients

had the comparatively favorable abnormalities inv-16, an inversion of the 16th chromosome, or t(8,21), a translocation between between chromosomes 8 and 21. Consequently, to take advantage of cytogenetics as a prognostic variable in our regression analyses, we grouped the abnormalities into three categories: poor (-5,-7), intermediate (diploid, -Y, or insufficient metaphases to classify) or good (+8, 11q, inv-16, t(8,21) or other). We used covariates for two different purposes: (i) to model the transition times (e.g. time to death, time between complete remission and death, etc.) in the likelihood-based method, and (ii) to model the probability of receiving the salvage treatment in the IPTW method (using logistic regression). To realize the first objective, we fit accelerated failure time models on 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 lognormal), 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 to the other sample values. Consequently, to ensure stability of the model fits, six of the seven component models were fit 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 Bayesian information criterion (BIC) for the 28 model combinations are shown in Table 2. For each time component, the best model was chosen to be that minimizing the BIC among the four AFT 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 lognormal for T^R and T^{PD} (Table 2), regardless of whether the outliers were included or excluded in the model fitting. We present the details of the model fits without outliers.

Table 2: Bayesian information criterion (BIC) for each of four different models fit to each transition time in the leukemia data set. For each transition time, the minimum BIC is underlined.

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

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. While such deaths may be attributed to either the leukemia or the chemotherapy, so called “regimen-related death,” due to the fact that both the disease and the treatment cause low WBC 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 death due to their poor prognosis at trial entry. The overall rate of death during induction chemotherapy was 33% (69/210), and the induction death rates across the four regimens varied from 28% to 38% (p-value = 0.70, generalized Fisher exact test). In the fitted model for the three event times during induction, summarized in Table 3, none of the baseline covariates were significantly associated with T^D . There did not appear to be any significant difference between the induction treatment effects on T^D , although ATRA seems to 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+ATRA (31% and 24% respectively) compared to those who received FAI+G or FAI+ATRA+G (7.8% and 10% respectively). The times to treatment resistance were similar across the four induction treatments, but with greater variability in the *FAI + G* arm (Table 3).

Among the 39 patients who were resistant to frontline treatment, 27 were given HDAC as salvage treatment. Two patients in this cohort were censored prior to observing death. In type

Table 3: Maximum likelihood estimates from AFT model for time to death, resistance, and complete remission during induction stage. Each parameter estimate is given with 95% confidence interval limits subscripted on the left and right.

Distribution	Time to		
	Death Weibull	Resistance Log-normal	CR Log-logistic
Intercept	2.803.79 _{4.80}	3.674.36 _{5.05}	3.103.38 _{3.65}
Frontline Therapy			
FAI	-0.150.29 _{0.73}	-0.230.13 _{0.50}	-0.130.05 _{0.22}
FAI+ATRA	-0.400.08 _{0.56}	-0.220.17 _{0.57}	-0.21 - 0.05 _{0.11}
FAI+G	-0.290.23 _{0.60}	-0.420.09 _{0.59}	-0.110.05 _{0.22}
FAI+G+ATRA	ref	-	-
Age (per year)	-0.02 - 0.005 _{0.01}	-0.016 - 0.007 _{0.002}	-0.00150.0023 _{0.006}
Cytogenetic Group*			
0 vs. 2	-0.57 - 0.13 _{0.30}	-0.22 - 0.11 _{0.43}	-0.22 - 0.08 _{0.05}
1 vs. 2	-0.57 - 0.17 _{0.24}	-0.130.04 _{0.21}	
σ	0.540.65 _{0.79}	0.300.38 _{0.47}	0.150.17 _{0.20}

*0 = (“DIP,-Y”, “IM”), 1=“-5,-7”, 2=(“+8”, “11Q”, “INV16”, “T(8,21)”, “MISC”).

3 likelihood ratio analysis, factors that were associated with time from induction treatment resistance to death were age, $\log(T^R)$, frontline therapy, HDAC as salvage (B_1) and their interaction (Table 4). Patients with older age, shorter T^R , frontline therapy $FAI+G+ATRA$, or salvage with $HDAC$ died more quickly following their disease being declared resistant. Among patients given non-HDAC salvage, T^{RD} was significantly greater if they received $FAI+ATRA$ or $FAI+G$ compared to those who received $FAI+G+ATRA$ as the induction treatment. Also, for patients receiving $FAI+G$ as induction and $HDAC$ as salvage following treatment resistance, T^{RD} was significantly larger than those who received $FAI+G$ but no $HDAC$ or $FAI+G+ATRA$ either with or without $HDAC$ salvage.

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 , $FAI+ATRA$, $FAI+G$ and $FAI+G+ATRA$ arms, respectively. Time to achieve CR did not differ significantly with frontline therapy (Table 3). 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 there were only 9 patients who died in CR, an intercept-only exponential AFT model was used for modeling T^{CD} . On the other hand, 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 4.

Cytogenetics and T^C were associated with T^{CP} . The longer it took to achieve CR, the shorter the period of time the patient remained in CR, a well-known phenomenon in chemotherapy for AML/MDS (Shen and Thall, 1998; Estey, Shen and Thall, 2000). Recall that cytogenetic abnormalities were classified as good (“+8”, “11Q”, “INV16”, “T(8,21)”,

Table 4: Maximum likelihood estimates from AFT 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}). Each parameter estimate is given with 95% confidence interval limits subscripted on the left and right.

Distribution	Time		
	T^{RD}	T^{CP}	T^{PD}
Intercept	-6.31 - 1.32 _{3.68}	6.498.11 _{9.73}	-0.721.25 _{3.23}
Frontline therapy			
FAI vs. FAI+G+ATRA	-0.570.64 _{1.85}	-0.420.17 _{0.76}	-0.86 - 0.21 _{0.45}
FAI+ATRA vs. FAI+G+ATRA	0.551.83 _{3.10}	-0.280.29 _{0.86}	-0.090.50 _{1.09}
FAI+G vs. FAI+G+ATRA	0.872.83 _{4.80}	0.030.62 _{1.21}	-0.300.27 _{0.84}
Cytogenetic Group*			
0 vs. 2	-0.770.29 _{1.36}	-0.340.03 _{0.41}	-0.56 - 0.05 _{0.45}
1 vs. 2	-0.460.49 _{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)	0.111.20 _{2.30}	-	-
log(Time to CR)	-	-1.29 - 0.83 _{-0.37}	-
log(Time to disease progression)	-	-	0.550.85 _{1.16}
Salvage therapy			
HDAC (vs. 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 (vs others)	-2.310.28 _{2.88}	-0.13 - 0.80 _{1.73}	
[FAI+ATRA]×HDAC (vs others)	-0.991.66 _{4.31}	-0.220.64 _{1.51}	
[FAI+G]×HDAC (vs others)	1.024.25 _{7.48}	0.371.20 _{2.03}	
Scale		0.340.40 _{0.49}	0.850.99 _{1.15}

*0 = (“DIP,-Y”, “IM”), 1=“-5,-7”, 2=(“+8”, “11Q”, “INV16”, “T(8,21)”, “MISC”).

“MISC”), intermediate (diploid, -Y or inevaluable) or poor (-5/-7). Patients with a “good” cytogenetic abnormality were 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. Older patients were likely to have shorter residual life once disease progressed, compared to 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 leukemia data were calculated using both the likelihood-based method and the IPTW method, from formulas (7) and (8), respectively. Confidence intervals for these estimates were calculated using a non-parametric bootstrap method based on 500 with-replacement samples. The results are presented in Table 5.4. The likelihood-based bootstrap confidence intervals are illustrated in Figure 2 using the data with outliers removed, and in Figure 3 using the entire data set.

It is clear from Table 5.4 that the two methods give very different estimates for mean overall survival time, with the likelihood-based estimator larger than the corresponding IPTW estimator for all strategies. This is not entirely surprising, since the likelihood-based method defines overall survival time in terms of the seven transition times via (1), as illustrated by Figure 1. Moreover, it uses regression models to account for effects of patient covariates and previous transition times, in addition to the treatments, on each transition time. In contrast, the IPTW estimator ignores this structure entirely, and uses the covariates only to estimate the strategy probability weights. The confidence intervals were also wider for the likelihood-

based estimators compared to the IPW estimators. This is due to the higher variability in the likelihood-based estimates, which is due mainly to the inclusion of covariates in modeling the component time-to-event variables. Additionally, modeling 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. In contrast, 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 frontline regardless of salvage, with the exception that under the likelihood-based analysis the strategy (FAI+G+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 Figures 2 and 3 for the likelihood-based approach, the mean overall survival estimates were largest for the four strategies with FAI+ATRA as frontline. With the likelihood-based approach, Figures 2 and 3 together show that the substantive conclusions were insensitive to whether the outliers were included or not, although using all of the data gave much smaller bootstrap confidence intervals for the means associated with the four strategies (FAI+G, 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 (i) FAI+ATRA was the best remission induction therapy, (ii) if the patient's disease was resistant to FAI+ATRA as induction therapy then it was irrelevant whether the salvage therapy contained HDAC, and (iii) if the patient achieved CR with FAI+ATRA and later relapsed then salvage with HDAC was superior. These conclusions, while 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+ATRA, FAI+G, or FAI+ATRA+G were significantly different from FAI alone with respect to either survival or event-free survival time, considering only the frontline therapies. An exhaustive formal comparison of the 16 strategies based on our analyses would require 120 pairwise tests, an unavoidable multiple comparisons problem that arises when evaluating multi-stage strategies. The trial was not designed to identify multi-stage strategies, and no clinical study can be powered to reliably conduct so many pairwise tests. With regard to estimation of strategy-specific mean survival times, however, although the 95% confidence intervals in Table 5 have a large degree of overlap, it is striking that the two strategies (FAI+ATRA, HDAC, HDAC) and (FAI+ATRA, OTHER, HDAC) appear to be superior based on both of the two very different analytic approaches that we have taken here.

6 Discussion

We have re-analyzed a data set from a four-arm clinical trial designed to assess the effects of adding ATRA, G, 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 multi-stage, adaptive nature of the therapy 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 tran-

Table 5: Strategy-specific estimates of mean overall survival time, in days, based on the IPTW and Likelihood-based methods. Each estimate is given with 95% confidence interval limits subscripted on the left and right.

Strategy	Estimators		
	IPTW	Likelihood-Based Excluding Outliers	Likelihood-Based Including Outliers
(A, B_1, B_2)			
$(FAI, HDAC, HDAC)$	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
$(FAI + G, HDAC, HDAC)$	251 ₃₃₇ 445	309 ₄₀₆ 1151	353 ₄₉₃ 757
$(FAI + G, HDAC, OTHER)$	217 ₃₀₇ 408	345 ₄₅₇ 1217	404 ₅₇₇ 850
$(FAI + G, OTHER, HDAC)$	253 ₃₃₈ 445	306 ₄₀₀ 1151	355 ₄₈₆ 755
$(FAI + G, OTHER, OTHER)$	218 ₃₀₉ 410	345 ₄₅₁ 1210	402 ₅₆₉ 847
$(FAI + G + ATRA, HDAC, HDAC)$	169 ₃₂₈ 514	246 ₃₄₃ 528	282 ₄₁₃ 661
$(FAI + G + ATRA, HDAC, OTHER)$	215 ₂₉₄ 367	285 ₃₉₆ 563	356 ₅₁₇ 824
$(FAI + G + ATRA, OTHER, HDAC)$	187 ₃₅₁ 546	281 ₃₈₁ 569	320 ₄₅₁ 700
$(FAI + G + ATRA, OTHER, OTHER)$	236 ₃₁₈ 392	324 ₄₃₄ 614	395 ₅₅₄ 863

Figure 2: Overall mean survival estimates and 95% 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, but if the patient’s disease is resistant to therapy, or if relapse occurs after achieving complete remission, then give HDAC as salvage.” 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.

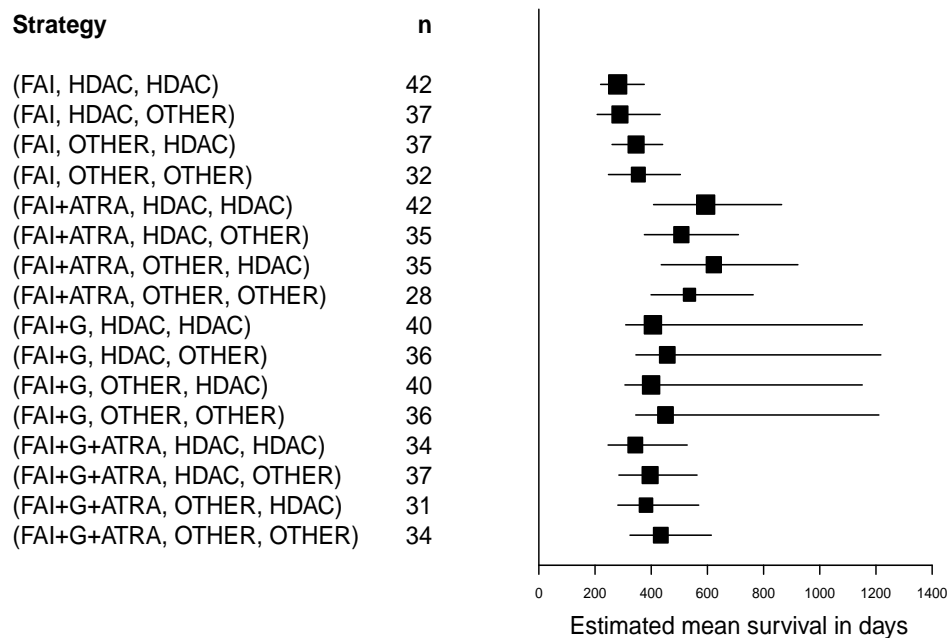
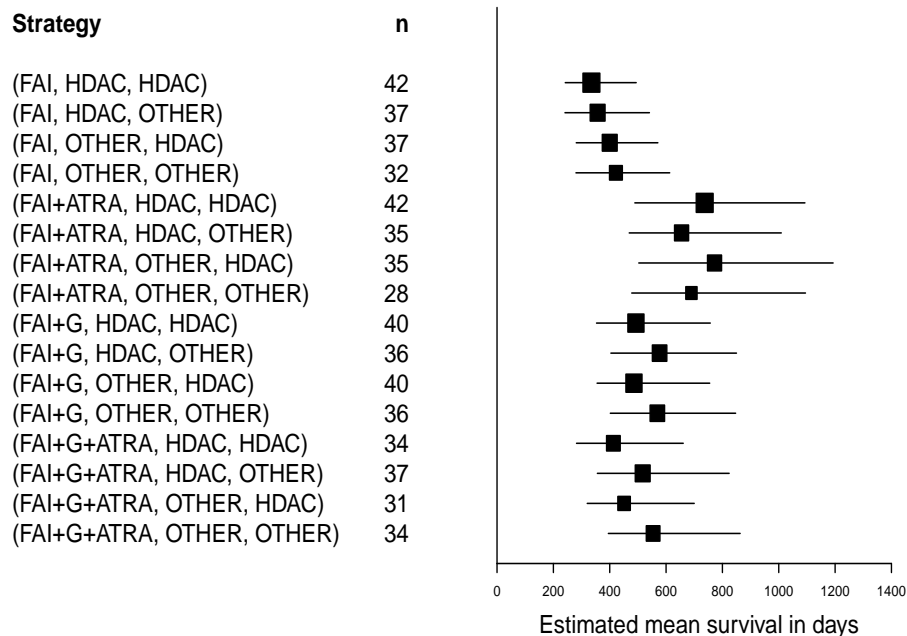


Figure 3: Overall mean survival estimates and 95% non-parametric bootstrap confidence intervals for estimators under the likelihood method based on all observations in the data set including putative outliers. Strategies such as (FAI,HDAC,HDAC) stand for “Give FAI as induction, but if the patient’s disease is resistant to therapy, or if relapse occurs after achieving complete remission, then give HDAC as salvage.” 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.



sition time. The second method employed IPTW-based estimating equations, and was much simpler, using covariates only to estimate the probabilities of the different strategies. While the two methods gave numerically different estimates of overall survival 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, a conclusion not seen earlier because only frontline treatments were evaluated. The trial was motivated by the idea that retinoids, such as ATRA, might improve outcome for AML/MDS patients when given with chemotherapy, since it was well established at the time this trial was initiated that ATRA has substantive anti-disease activity in treating acute promyelocytic leukemia (Estey, et al., 1997). Based on our re-analyses of this data set, it seems that this idea for treatment of AML/MDS may have been correct. While our results cannot be considered confirmatory, it seems that analyses of the types presented here, had they 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 frontline and salvage chemotherapy combinations for AML/MDS may improve overall survival time. More generally, our analyses of this data set strongly suggest that a great deal of valuable information may be lost when using conventional methods based on initial treatment alone to analyze clinical trials.

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