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A Markov analysis of azacitidine and venetoclax vs induction chemotherapy for medically fit patients with AML

Mithunan Ravindran,[1] Lee Mozessohn,[1,2] Matthew Cheung,[1,2] Rena Buckstein,[1,2,*] and Jennifer Teichman[1,2,*]

[1]Department of Medicine, University of Toronto, Toronto, ON, Canada; and [2]Division of Medical Oncology and Hematology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Key Points

- Medically fit patients with newly diagnosed adverse-risk AML may benefit from treatment with aza-ven (IC, 1.4 QALYs vs aza-ven, 2.0 QALYs).
- IC remains the preferred induction regimen for patients with intermediate-risk AML.

Although induction chemotherapy (IC) is the standard of care in medically fit patients with newly diagnosed acute myeloid leukemia (AML), limited retrospective data indicate that patients at adverse-risk may benefit from azacytidine and venetoclax (aza-ven). Our goal was to perform a Markov decision analysis to determine whether IC or aza-ven is the optimal induction regimen in this population. Using the TreeAge software, Markov models were created for adverse-risk and intermediate-risk cohorts. A systematic review of the literature informed the transition probabilities and utilities included in the analyses. Our primary outcome was quality-adjusted life years (QALYs) gained over 5 years after diagnosis. Overall, patients at adverse risk treated with IC gained 1.4 QALYs, compared with 2.0 QALYs in patients treated with aza-ven. Patients at adverse risk treated with IC and allogeneic stem cell transplantation (allo-SCT), IC, aza-ven and allo-SCT, or aza-ven gained 2.1, 1.5, 3.0, and 1.9 QALYs, respectively. Meanwhile, patients at intermediate risk treated with IC gained 2.0 QALY, compared with 1.7 QALY in patients treated with aza-ven. Patients at intermediate risk treated with IC and allo-SCT, IC, aza-ven and allo-SCT, and aza-ven gained 2.7, 2.3, 2.6, and 1.8 QALYs, respectively. We have demonstrated that medically fit patients with newly diagnosed adverse-risk AML may benefit from treatment with aza-ven over those treated with IC, whereas IC remains the preferred approach for patients at intermediate risk. Our work challenges the use of the European LeukemiaNet risk classification for patients treated with aza-ven and highlights the need for prospective investigation into aza-ven as induction therapy for medically fit patients.

Introduction

Induction chemotherapy (IC) is the standard of care for younger, medically fit patients with newly diagnosed acute myeloid leukemia (AML).[1] It is well established that IC is an intensive chemotherapeutic regimen that requires prolonged hospitalization and carries a significant risk of morbidity and mortality. Age, comorbidities, performance status, and frailty are all assessed to determine whether a patient would benefit from IC.[2,3] Typically, IC is not offered to those aged >75 years, which presents a significant challenge, given that the median age at diagnosis of AML is 69 years.[4]

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*R.B. and J.T. are joint senior authors.

Data are available on request from the corresponding author, Rena Buckstein (rena.buckstein@sunnybrook.ca).

The full-text version of this article contains a data supplement.

Historically, older or unfit patients with AML were treated with hypomethylating agents (eg, azacitidine [aza]), other nonintensive therapies such as low-dose cytarabine, or best supportive care.[5] VIALE-A, a recent phase 3, multicenter randomized controlled trial compared aza combined with the B-cell lymphoma 2 protein inhibitor venetoclax (aza-ven) with aza alone.[6] Aza-ven was found to have a significantly greater composite complete remission (CR) rate (66.4% vs 28.3%) and a significant improvement in overall survival (OS; (14.7 months vs 9.6 months).

The median age of the VIALE-A population was 76 years, and, by trial design, these patients were ineligible for treatment with IC. Whether IC or aza-ven is a superior approach to achieving CR and proceeding to allogeneic stem cell transplantation (allo-SCT) in medically fit patients remains unknown. A retrospective cohort study comparing IC and aza-ven found an unadjusted median OS of 884 days vs 483 days, respectively.[7] In the unadjusted analysis, the patients treated with aza-ven were unsurprisingly older and more comorbid. However, in a propensity-matched analysis, patients with adverse-risk AML were found to have a preferential benefit when treated with aza-ven.[7]

Randomized controlled trials comparing these regimens are ongoing, with results expected in 2026.[8] In the interim, an evidence-based decision tool that enables risk-stratified comparisons between IC and aza-ven would be valuable. The objective of this study was to perform a Markov decision analysis to determine the optimal induction regimen (IC vs aza-ven) for a theoretical cohort of medically fit IC-eligible patients with newly diagnosed AML.

Methods

Selection of a Markov model

A Markov model was selected for our analysis because this approach effectively accounts for risk that varies over the study period (eg, risk of relapse is present throughout our 5-year study period but is different at year 1 vs year 5).[9] This analysis is particularly useful for AML, in which relapse within year 1 is prognostically different from relapse at year 5, and the timing of relapse has a major impact on the quality-adjusted life years (QALYs) accrued. Additionally, Markov models effectively capture events that can occur multiple times within the study period (eg, relapse).[9] Please see supplemental Materials for further details regarding the construction of our Markov model.

There is precedent for the use of Markov analyses in hematology. Cutler et al[10] examined the optimal timing of allo-SCT for patients with myelodysplastic syndrome, and Kurosawa et al[11] studied allo-SCT vs chemotherapy for patients with AML who had achieved first remission. Markov analyses have also been used to assess the cost-effectiveness of different treatment approaches. Yamamoto et al[12] compared the incremental cost-effectiveness ratio of various tyrosine kinase inhibitors for the treatment of CML, and Slot et el[13] compared the incremental cost-effectiveness ratio of venobinutuzumab vs ibrutinib for the treatment of chronic lymphocytic leukemia.

Patients and interventions

A systematic review of the literature was conducted to inform the probabilities of each outcome within the Markov analyses. Specifically, PubMed, Medline, and Embase were searched for prospective or retrospective studies reporting the outcomes of patients with newly diagnosed AML treated with IC or aza-ven, with or without allo-SCT. Reference lists of relevant studies as well as abstracts from the most recent meeting of the American Society of Hematology were manually reviewed to identify studies not extracted in the systematic search. Given the target population of patients eligible for IC, emphasis was placed on studies with a median age of between 60 and 70 years.

Model design

Using the TreeAge Pro Healthcare modeling software (version 2023 R1.2), 2 Markov models were generated: 1 for patients at adverse risk and 1 for patients at intermediate risk. Patients were stratified based on the 2017 European Leukemia Network classification system.[14,15] A model for favorable-risk disease was omitted, given a paucity of data on the use of aza-ven in this group and the superior outcomes with IC in younger patients with favorable-risk disease.

A simplified schematic of the Markov model is shown in Figure 1. Each model examines 2 theoretical cohorts of 1000 patients with newly diagnosed AML: 1 cohort comprising patients treated with IC and the other comprising patients treated with aza-ven. Disease states after induction included composite CR (CR, or CR with incomplete hematologic recovery), primary refractory disease (no CR after 2 courses of intensive induction treatment), or early death (from any cause within 30 days).[14-16] Those who achieved CR either did or did not receive allo-SCT, and both groups either remained in disease-free survival (DFS), transitioned to relapse, or proceeded to death (from any cause after 30 days). Patients who relapsed either transitioned to a second CR (CR2) or died. Patients with primary refractory disease either transitioned to CR or died. Our primary outcome was the QALYs gained over a time horizon of 5 years after initial diagnosis.

Transition probabilities

Five-year OS and relapse-free survival curves extracted from the literature search were digitized to allow for accurate year-to-year variability in risk of death and relapse, respectively. Other discrete events, such as the proportion of patients who achieve CR proceeding allo-SCT, were reported as a single value. A final weighted average accounting for the sample sizes from the referenced studies was calculated for each variable and used in the model. The final weighted data used for the adverse-risk and intermediate-risk models can be found in Table 1.

Health utilities

Each disease state was assigned a QALY utility derived from the literature (eg, adverse-risk AML DFS vs relapsed disease). The Markov model determined how many patients were in a particular disease state and for how long. Thus, the QALYs gained in the IC arm was compared with that in the aza-ven arm, for both adverse- and intermediate-risk disease. The QALY utilities for patients treated with IC and aza-ven were identified as part of our systematic review and can be found in Table 2.

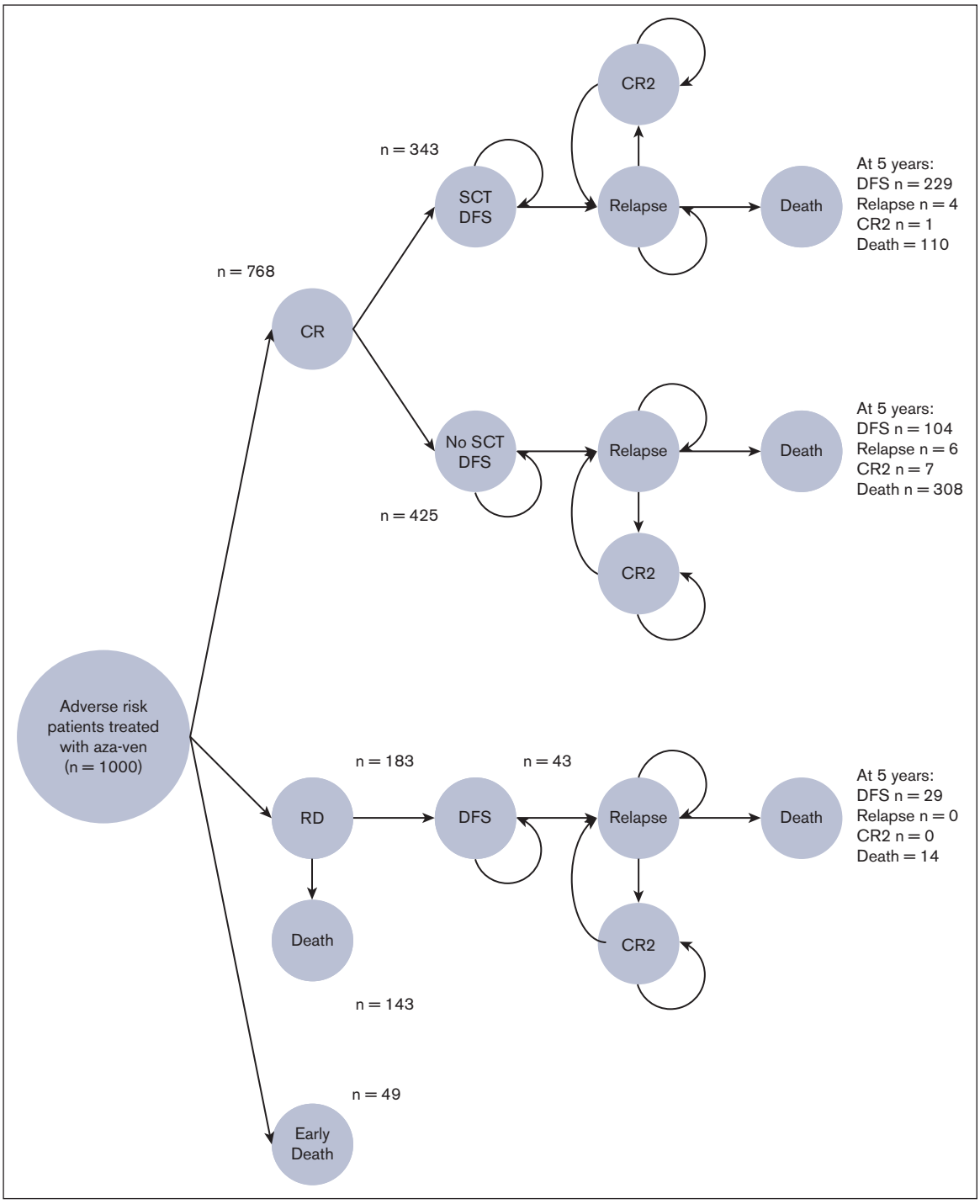

Figure 1. A simplified schematic of the Markov model design. This figure outlines the health states included in the analysis and the possible transitions over time. CR, composite complete remission; RD, refractory disease.

Sensitivity analyses

One-way sensitivity analyses were generated for each variable included in the model, and threshold values were reported. If the threshold value was not clinically plausible, then the analysis was considered insensitive to that variable.

Results

Patient characteristics

Based on weighted averages from the studies included in our analysis, in the adverse-risk model, the median age of patients

Table 1. Patient demographics by weighted averages

Adverse-risk model			Intermediate-risk model		
Variable	**Aza-ven**	**IC**	**Variable**	**Aza-ven**	**IC**
Age, y	66.9	58.3	Age, y	72.4	55.2
Male (%)	0.517	0.528	Male (%)	0.57	0.486
Female (%)	0.483	0.472	Female (%)	0.43	0.514
Bone marrow blasts (%)	0.502	0.66	Bone marrow blasts (%)	0.5	0.809
Secondary AML (%)	0.459	0.082	Secondary AML (%)	0.3	0.09
Treatment-related AML (%)	0.212	0.07	Treatment-related AML (%)	0.264	0.06

treated with aza-ven or IC was 67 and 58 years, respectively. In the intermediate-risk group, the median age of patients treated with aza-ven or IC was 72 and 55 years, respectively.

Adverse-risk analysis

Among patients with adverse-risk AML, aza-ven was superior to IC for the primary outcome. Overall, patients treated with IC gained 1.42 QALYs over 5 years from the time of diagnosis, compared with 1.97 QALYs among patients treated with aza-ven. On subgroup analysis, patients who achieved CR with IC gained 2.15 QALYs after proceeding to allo-SCT vs 1.50 QALYs without allo-SCT. Those treated with aza-ven in CR gained 3.00 QALYs after allo-SCT compared with 1.92 QALYs without allo-SCT.

Figures 2A-D shows how the proportions of patients with adverse-risk disease in states of DFS, relapse, CR2, or death changed over 5 years. For patients treated with IC who underwent allo-SCT, mortality was 42.3% and 59.0% at 1 and 5 years, respectively (Figure 2A). For patients treated with IC without allo-SCT, mortality was 56.4% and 79.8% at 1 and 5 years, respectively (Figure 2B). For patients treated with aza-ven who underwent allo-SCT, mortality was 15.2% and 32.0% at 1 and 5 years, respectively (Figure 2C), whereas for those who did not undergo allo-SCT, mortality was 42% and 72.4% at 1 and 5 years, respectively (Figure 2D).

Intermediate-risk analysis

Among patients with intermediate-risk AML, IC was superior to aza-ven for the primary outcome. Overall, patients treated with IC gained 2.05 QALYs, compared with 1.69 QALYs among patients treated with aza-ven. Patients who achieved CR with IC followed by allo-SCT gained 2.74 QALYs, whereas those who did not receive allo-SCT gained 2.35 QALYs. Patients who achieved CR with aza-ven followed by allo-SCT gained 2.59 QALYs, whereas those who did not receive allo-SCT gained 1.84 QALYs. Health utilities values for both the adverse and intermediate risk models can be found in Table 3.

Figure 3A-D shows how the proportions of patient with intermediate-risk AML in states of DFS, relapse, CR2, or death changed over 5 years. For patients treated with IC who underwent allo-SCT, mortality was 28.3% and 43.5% at 1 and 5 years, respectively (Figure 3A). For patients treated with IC without allo-SCT, mortality was 39.2% and 55.5% at 1 and 5 years, respectively (Figure 3B). For patients treated with aza-ven who underwent allo-SCT, mortality was 36.8% and 40.0% at 1 and 5 years, respectively (Figure 3C), whereas in those who did not proceed to allo-SCT, mortality was 44.4% and 72.0% at 1 and 5 years, respectively (Figure 3D).

Sensitivity analyses

The 1-way sensitivity analysis threshold values for each of the variables included in both the adverse and intermediate-risk analyses are shown in Table 4. Although the base-case analysis favored aza-ven in the adverse-risk group, IC was favored if >44% of patients treated with aza-ven and allo-SCT died within the first year or if the aza-ven DFS health utility was <0.56. Similarly, although the base-case analysis favored IC in the intermediate-risk group, aza-ven was favored if the proportion of patients treated with IC and allo-SCT who died within the first year was >39% or if the IC DFS health utility was <0.68.

Discussion

Using a Markov analysis, we demonstrate that induction-eligible patients with newly diagnosed adverse-risk AML may benefit from treatment with aza-ven over IC. Conversely, our model indicates that IC remains the preferred approach for patients with intermediate-risk AML.

Our results are aligned with previously reported data from a propensity-matched analysis with a robust sample size (IC, n = 149; aza-ven, n = 143).[7] The authors demonstrated improved OS among patients with adverse-risk disease treated with aza-ven, whereas those with intermediate-risk disease had improved OS if treated with IC. Our results mirror these data with regard to QALYs. Over 5 years, patients with adverse-risk disease treated with aza-ven gained 1.97 QALYs compared with 1.42 QALYs among those treated with IC. Conversely, patients with intermediate-risk disease treated with IC gained 2.05 QALYs compared with 1.69 QALYs among those treated with aza-ven.

In another recent retrospective, propensity-matched analysis comparing OS and DFS of patients (median age, 69 years) treated with IC vs aza-ven, intermediate-risk disease favored IC, whereas TP53-mutated AML favored aza-ven.[32] This study was omitted from our model because the majority of patients in both the IC and aza-ven arms (58.7% and 63.0%, respectively) had unknown cytogenetics. The authors of that study reported no statistically significant differences in OS and DFS between IC and aza-ven, despite a higher rate of CR in the IC group. Although it is challenging to interpret these results with substantial missing cytogenetic data, the findings support a subgroup of patients at higher risk who may benefit from treatment with aza-ven.

We selected a Markov design rather than a propensity score matched analysis because the former enables a sophisticated estimation of QALY accrued. Markov models are inherently

Table 2. Health state transition probabilities for the adverse- and intermediate-risk Markov decision analyses

Health state probability	Weighted average	References
Adverse-risk model		
Relapse with AZ and SCT (year-by-year data)	0.227, 0.030, 0, 0, and 0	Pollyea et al[17] and Winters et al[18]
Death after relapse with AZ and SCT	0.62	Pollyea et al[17] and Salhotra et al[19]
Death within the first year of AZ and SCT	0.152	Pollyea et al,[17] Winters et al,[18] and Salhotra et al [19]
SCT after induction with AZ	0.343	Cherry et al,[7] Pollyea et al,[17] and Salhotra et al [19]
No SCT after induction with AZ	0.425	Cherry et al,[7] Pollyea et al,[17] and Salhotra et al[19]
Early death with AZ	0.049	Cherry et al[7]
Relapse with AZ and no SCT (year-by-year data)	0.51, 0.28, 0.2, 0.18, and 0	Cherry et al[7]
Death after relapse with AZ and no SCT	0.784	Garciaz et al[20] and Johnson et al[21]
Death within the first year of AZ and no SCT	0.42	Cherry et al[7]
Composite CR with AZ after primary refractory disease	0.216	Garciaz et al[20] and Johnson et al[21]
Relapse with IC and SCT (year-by-year data)	0.507, 0.147, 0.106, 0, and 0.158	Bataller et al,[22] Herold et al,[23] and Hansen et al[24]
Death after relapse with IC and SCT	0.727	Burnett et al[25] and Herold et al[23]
Death within the first year of IC and SCT	0.423	Bataller et al,[22] Herold et al,[23] Hansen et al[24]
SCT after induction with IC	0.351	Bataller et al,[22] Burnett et al,[25] and Lo et al[26]
No SCT after induction with IC	0.355	Bataller et al,[22] Burnett et al,[25] and Lo et al[26]
Early death with IC	0.102	Bataller et al[22]
Relapse with IC and no SCT (year-by-year data)	0.652, 0.352, 0.110, 0.120, and 0	Herold et al[23] and Burnett et al[25]
Death after relapse with IC and no SCT	0.794	Herold et al[23] and Burnett et al[25]
Death within the first year of IC and no SCT	0.564	Herold et al[23] and Rausch et al[27]
Composite CR with IC after primary refractory disease	0.66	Bataller et al[22]
Intermediate-risk model		
Relapse with AZ and SCT (year-by-year data)	0.42, 0, 0, 0, 0	Pasvolsky et al[28]
Death after relapse with AZ and SCT	0.421	Pasvolsky et al[28]
Death within the first year of AZ and SCT	0.368	Pasvolsky et al[28]
SCT after induction with AZ	0.317	Pollyea et al,[29] Pollyea et al,[17] and Salhotra et al[19]
No SCT after induction with AZ	0.392	Pollyea et al,[29] Pollyea et al,[17] and Salhotra et al[19]
Early death with AZ	0.049	Cherry et al[7]
Relapse with AZ and no SCT (year-by-year data)	0.507, 0.432, 0.129, 0, 0	Pollyea et al[29] and DiNardo et al[5]
Death after relapse with AZ and no SCT	0.763	Garciaz et al[20] and Johnson et al[21]
Death within the first year of AZ and no SCT	0.444	Pollyea et al[29] and DiNardo et al[5]
Composite CR with AZ after primary refractory disease	0.237	Garciaz et al[20] and Johnson et al[21]
Relapse with IC and SCT (year-by-year data)	0.359, 0.111, 0.088, 0.046, and 0.018	Batalleret al,[22] Herold et al,[23] and Hansen et al [24]
Death after relapse with IC and SCT	0.576	Burnett et al[25] and Herold et al[23]
Death within the first year of IC and SCT	0.283	Bataller et al,[22] Herold et al,[23] and Hansen et al[24]
SCT after induction with IC	0.263	Bataller et al,[22] Burnett et al,[25] and Lo[26] ASH 2022
No SCT after induction with IC	0.535	Bataller et al,[22] Burnett et al,[25] and Lo[26] ASH 2022
Early death with IC	0.119	Bataller et al[22]
Relapse with IC and no SCT (year-by-year data)	0.394, 0.210, 0.083, 0.065, 0.030	Herold et al[23] and Burnett et al[25]
Death after relapse with IC and no SCT	0.674	Herold et al[23] and Burnett et al[25]
Death within the first year of IC and no SCT	0.392	Herold et al[23] and Rausch et al[27]
Composite CR with IC after primary refractory disease	0.667	Bataller et al[22]

AZ, azacitidine and venetoclax

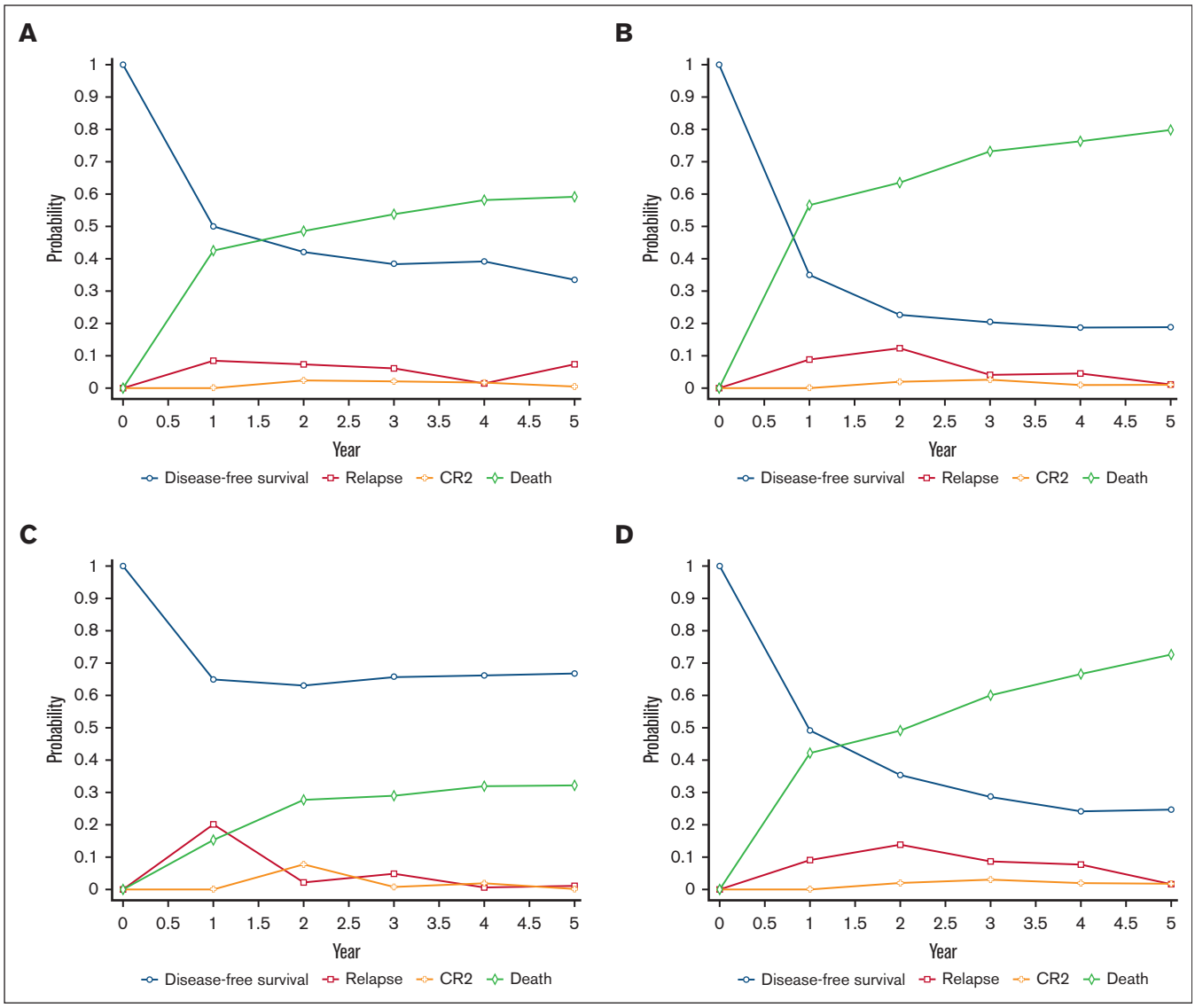

Figure 2. Rates of DFS, relapse, CR2, and death over 5 years from the time of AML diagnosis for patients with adverse-risk disease. (A) IC and allo-SCT, (B) IC without allo-SCT, (C) aza-ven and allo-SCT, and (D) aza-ven without allo-SCT.

capable of generating DFS and OS data (Figure 2A-D); however, improved QALYs is the standard primary outcome for both clinically oriented and cost-effectiveness Markov analyses.[10,11] Markov analyses are uniquely positioned to evaluate the length of time a patient remains in a given health state and apply the relevant QALY for that duration. This provides an additional layer of clinical relevance by incorporating patient experience and comorbidity that may not be captured by the limited variables incorporated in the model. For example, QALY better captures the experience of a prolonged hospital admission for IC, compared with outpatient treatment for aza-ven. Additionally, propensity score matched analyses reporting DFS and OS alone would fail to capture sequential relapses within the same patient, and the differences in quality of life associated with transitions between these health states. One limitation of a Markov analysis compared with a propensity score matched analysis is that the latter would create matched cohorts of patients treated with either IC or aza-ven by virtue of similar propensity scores.[33] This allows for a balanced distribution of measured covariates in an observational study.

Our model produces results that are reflective of real-world data. For example, comparing the results of the adverse-risk cohort treated with IC and allo-SCT from Bataller et al with our results revealed a 1-year DFS of 48.0% vs 49.3%, 1-year mortality of 43.8% vs 42.3%, 5-year DFS of 33.0% vs 33.4%, and 5-year mortality 62% vs 59%, respectively.[22] This association is strong despite using weighted averages from multiple sources. There was generally good agreement between different sources for the probability of the same variable, as can be seen in Table 2.

Although there are recent but limited QALY utility data available for aza-ven, we elected to incorporate the single agent aza QALY utility values. The aza QALY utility data have been published in the literature for longer, so there is more clinical experience with these values, and they have been used in cost-effectiveness analyses.[30]

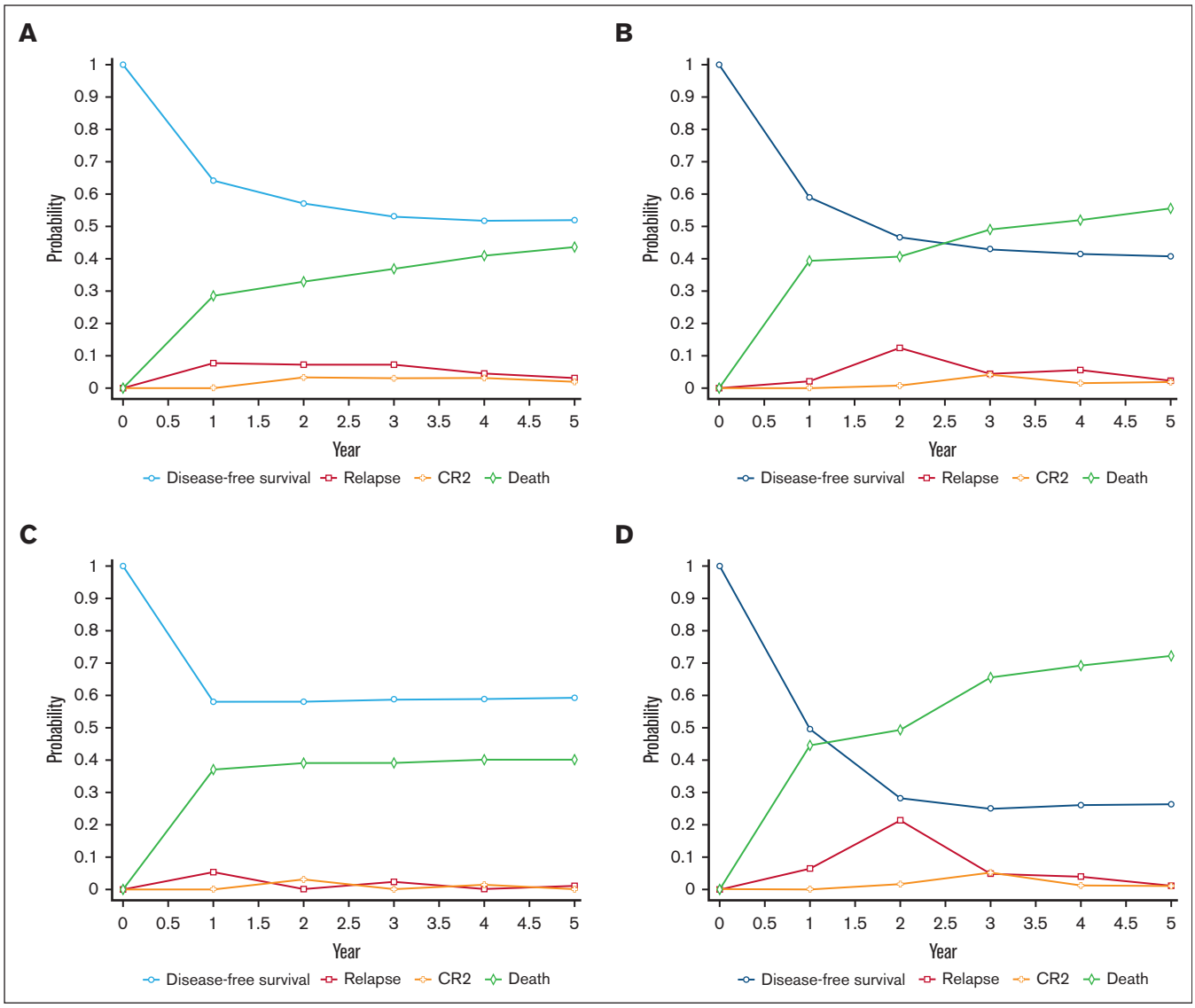

Figure 3. Rates of DFS, relapse, CR2, and death over 5 years from the time of AML diagnosis for patients with intermediate-risk disease. (A) IC and allo-SCT, (B) IC without allo-SCT, (C) aza-ven and allo-SCT, and (D) aza-ven without allo-SCT.

This extrapolation is based upon results from VIALE-A, which reported no differences between the aza and aza-ven in terms of quality of life.[6,30] The aza-ven QALY values reported in 2 studies were challenging to reconcile with our clinical experience, particularly because the high-utility values (0.733 and 0.723) for the relapse state were so similar to the utility values of 0.815 and 0.796 for DFS in the same studies.[34,35]

Table 3. Health utilities for the adverse- and intermediate-risk Markov decision analyses

Utility	Value	References
Adverse- and intermediate-risk model		
DFS if treated with AZ	0.8	Patel et al[30]
Relapse if treated with AZ	0.67	Patel et al[30]
DFS if treated with IC	0.83	Tremblay et al[31]
Relapse if treated with IC	0.53	Tremblay et al[31]

AZ, azacitidine and venetoclax

Our models carry several limitations. As an analysis of largely retrospective data, it was not possible to create IC and aza-ven cohorts with an equal distribution of key demographic and disease-specific characteristics. Given that IC is the standard of care in medically fit individuals, there are more robust data available for younger patients. In the current treatment landscape, aza-ven is primarily offered to patients with comorbidities that preclude them from receiving IC, so data are predominantly only available for older patients. The average age of patients receiving IC in our analysis was less than that of patients receiving aza-ven (adverse-risk IC, 58 years vs aza-ven, 67 years; intermediate-risk IC, 55 years vs aza-ven, 72 years), so these patients were likely more fit. Thus, the QALYs gained by patients in both the adverse- and

Table 4. Threshold values for the 1-way sensitivity analyses from the adverse- and intermediate-risk Markov models

Health state probability or utility	Adverse-risk favors IC	Intermediate-risk favors AZ
Relapse with AZ and SCT	–	–
Death after relapse with AZ and SCT	–	–
Death within the first year of AZ and SCT	>0.44	<0.05
SCT after induction with AZ	<0.11	>0.5
Relapse with AZ and no SCT	–	–
Death after relapse with AZ and no SCT	–	–
Death within the first year of AZ and no SCT	–	<0.05
Composite CR with AZ after primary refractory disease	–	>0.8
Relapse with IC and SCT	–	>0.89
Death after relapse with IC and SCT	–	–
Death within the first year of IC and SCT	<0.01	>0.39
SCT after induction with IC	–	<0.07
Relapse with IC and no SCT	–	>0.82
Death after relapse with IC and no SCT	–	–
Death within the first year with IC and no SCT	<0.02	–
Composite CR with IC after primary refractory disease	–	–
Health utility of DFS if treated with AZ	<0.56	>0.98
Health utility of relapse if treated with AZ	–	–
Health utility of DFS if treated with IC	–	<0.68
Health utility of relapse if treated with IC	–	–

AZ, azacitidine and venetoclax

intermediate-risk IC-treated cohort are likely inflated relative to those of their counterparts treated with aza-ven. Furthermore, among patients who underwent SCT, there was a strong selection bias in favor of those who were medically fit, so the improved survival and QALY outcomes they experienced were not due to this intervention alone.

Another limitation of our analysis is that few studies reported Eastern Cooperative Oncology Group performance status; the Charlson Comorbidity Index; or AML-specific comorbidity indices, such as the AML comorbidity index, the hematopoietic cell transplantation comorbidity index, or the AML composite model (AML-CM).[36-38] This introduces bias into our results because older but fit patients might have received aza-ven on the basis of age alone, and younger but unfit patients might have received IC because of discomfort using aza-ven in a currently off-label manner. An example of this would be the effect of comorbidity data on our intermediate-risk model. The 1-way sensitivity analysis for death within the first year in patients treated with IC followed by SCT identified a threshold value of 39%. Thus, if 1-year mortality in these patients exceeded 40%, the intermediate model would actually favor treatment with aza-ven over IC. Given that patients with high comorbidity had much greater mortality within the first year (15% among those with an AML-CM score of 1-4 vs 80% among those with a score > 10), our intermediate-risk model is indeed sensitive to differences in comorbidity as captured by the AML-CM. The impact of formally reported AML-specific comorbidity measures on our QALY outcomes would be an important area for further research, as much of these data predate the aza-ven era.

Finally, most of the patients included in our analysis were from the United States and Europe, which may not capture the global experience. Although there was generally a strong agreement between different sources for the probability of a particular variable in our data, this is likely not the case in all jurisdictions.

Our results contribute to a growing body of literature indicating that the 2017 European Leukemia Network risk stratification is not necessarily prognostic in patients treated with a combination of hypomethylating agent and ven.[16,39] An area of particular interest is the efficacy of aza-ven in isocitrate dehydrogenase 1/2 (IDH1/2)-mutated AML (~8% and ~12% of AML cases, respectively). The prognostic implications of IDH1/2 mutations have yet to be fully elucidated, with either favorable[40,41] adverse,[42-44] or uncertain prognosis.[45,46] Current literature would suggest that these different prognoses arise on the basis of submutations or comutations.[42] Pollyea et al found that patients with IDH1/2 mutations treated with aza and ven had a composite CR rate of 79% as well as a median duration of remission of 29.5 months and a median OS of 24.5 months.[47] Notably, patients with IDH1/2-mutated disease had superior OS compared with the wild-type cohort. VIALE-A also reported favorable hazard ratios for patients treated with aza-ven with respect to death of 0.28, 0.34, and 0.34 for IDH1, IDH2, and IDH1/2, respectively, compared with patients treated with aza alone.[6] Recent work demonstrated that the combination of the IDH1 inhibitor ivosidenib and aza resulted in a statistically significant increase in DFS and OS compared with aza alone.[48] Although the literature on aza-ven in patients with IDH1/2 mutations are limited, this represents an important future application of our model.

Another AML subgroup of interest is patients with FMS-like tyrosine kinase 3 (FLT3) mutations, particularly those with FLT3–internal tandem duplication mutations, given their poor prognosis and high risk of relapse.[49] Konopleva et al, however, did not find a significant difference in outcomes between patients with FLT3-mutated disease and those with wild-type disease treated with aza-ven.[50] Similarly, although VIALE-A did report a hazard ratio of 0.66 of death for FLT3 in favor of aza-ven, the 95% confidence interval was not significant at 0.35 to 1.26. That being said, recent data have reported that patients with FLT3-mutated disease had superior OS when treated with hypomethylating agent, ven, and FLT3 inhibitor (triplet therapy) compared with hypomethylating agent and FLT3 inhibitor alone (doublet therapy).[51] Taken together, further research into less-intensive cocktails personalized to mutational status will provide important opportunities to refine our model.

Our results, although derived from a modeled analysis of largely retrospective data, raise important questions about the use of aza-ven in medically fit patients. Patients with adverse-risk AML may preferentially gain a QALY benefit from treatment with aza-ven. The comparison in the intermediate-risk cohort is more limited given that IC remains the standard of care in this population, and, thus, the aza-ven data are derived from older, less medically fit patients. Future work should be aimed at prospectively evaluating the efficacy of aza-ven in medically fit patients with newly diagnosed AML.

Authorship

Contribution: R.B. conceptualized the study; M.R., L.M., M.C., R.B., and J.T. were responsible for the study methodology; M.R. and J.T. were responsible for formal analysis and investigation, and writing the original manuscript draft; M.R., L.M., M.C., R.B., and J.T. were responsible for reviewing and editing the manuscript; and R.B. supervised the study.

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ORCID profiles: L.M., 0000-0003-3436-3849; J.T., 0000-0002-7538-5772.

Correspondence: Rena Buckstein, Division of Medical Oncology and Hematology, Odette Cancer Center, Sunnybrook Health Sciences Center, 2075 Bayview Ave, T2-042, Toronto, ON M4N 3M5, Canada; email: rena.buckstein@sunnybrook.ca.

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