Published in final edited form as:

Leukemia. 2014 February ; 28(2): 289–292. doi:10.1038/leu.2013.176.

Declining Rates of Treatment-Related Mortality in Patients with Newly-diagnosed AML Given "Intense" Induction Regimens: A Report from SWOG and MD Anderson

Megan Othus[1], **Hagop Kantarjian**[2], **Stephen Petersdorf**[1], **Farhad Ravandi**[2], **John Godwin**[3], **Jorge Cortes**[2], **Sherry Pierce**[2], **Harry Erba**[4], **Stefan Faderl**[2], **Frederick R. Appelbaum**[1], and **Elihu Estey**[1]

[1]Fred Hutchinson Cancer Research Center and University of Washington, Seattle WA

[2]MD Anderson Cancer Center, Houston TX

[3]Loyola University, Chicago IL

[4]University of Alabama, Birmingham AL

Abstract

Less-intense remission induction regimens for adults with newly-diagnosed AML aim to reduce treatment-related mortality (TRM), here defined as death within 4 weeks after starting induction therapy. This assumes that TRM rates are similar to the 15-20% observed 20 years ago. Herein we test this assumption.

We examined TRM rates in 1409 patients treated on SWOG trials and 1,942 patients treated at MD Anderson (MDA) from 1991-2009. 88% of the SWOG received "3+7" or regimens of similar intensity while 92% of the MDA patients received ara-C at 1.5-2.0g/m2 daily × 3-5 days + other cytotoxic agents. We examined the relationship between time and TRM rates after accounting for other covariates.

TRM rates between 1991 and 2009 decreased from 18- 3% in SWOG and 16%- 4% at MDA. Multivariate analyses showed a significant decrease in TRM over time (p=0.001). The decrease in TRM was not limited to younger patients, those with a better performance status, or a lower WBC count.

Though our observations are limited to patients treated with intensive therapy at SWOG institutions and MDA, the decrease in TRM with time emphasizes the problem with historical controls and could be considered when selecting AML induction therapy.

Corresponding author: Megan Othus • mothus@fhcrc.org • 1100 Fairview Ave N • Seattle, WA 98109 • Phone (206) 667-5749• FAX (206) 667-7004.

Author Contributions: Megan Othus: analyzed and interpreted data, performed statistical analysis, principal writer, corresponding author; Hagop Kantarjian: data collection, data interpretation, manuscript writing; Stephen Petersdorf: data collection, data interpretation, manuscript writing; Farhad Ravandi: data collection, data interpretation, manuscript writing; John Godwin: data collection, data interpretation, manuscript writing; Jorge Cortes: data collection, data interpretation, manuscript writing; Sherry Pierce: data collection, manuscript writing; Harry Erba: data collection, data interpretation, manuscript writing; Stefan Faderl: data collection, data interpretation, manuscript writing; Frederick R. Appelbaum: analyzed and interpreted data, aided in writing, administrative support; Elihu H. Estey: designed research, analyzed and interpreted data, manuscript writing.

Conflicts of interest: The authors have no conflict of interest to disclose.

Keywords

AML; induction therapy; treatment related mortality; 3+7; high dose cytarabine; age groups; time trend; supportive care

Introduction

Death during remission induction ("treatment related mortality", TRM) is a well-known complication of therapy of acute myeloid leukemia (AML). Although TRM is more common with advancing age, performance status has been shown to be more closely associated with TRM than age (1,2), and TRM rates greater than 30% have been reported in older patients with poor performance status given standard induction therapy ("3+7") (2). Numerous other covariates also modulate the age effect on TRM (2,3). A desire to reduce TRM rates below those seen with 3+7 has motivated the introduction, primarily for older patients, of various regimens considered "less intense" than 3+7; examples include "low dose" ara-C (4), and, more recently, azacitidine (5,6,7) and decitabine (8,9).

This development assumes that TRM rates during AML with 3+7 have changed little with time. Some doubt has been cast on this assumption by the advent of newer supportive care measures. Perhaps consequent to their introduction, rates of non-relapse mortality after both ablative and reduced-intensity allogeneic hematopoietic cell transplant (HCT) have fallen considerably (10). This observation led us to speculate that the same has occurred with AML induction therapy. Accordingly we conducted an analysis of 3,351 adults with AML registered to clinical trials between 1991 and 2009 to examine if and how TRM rates changed over time. To see if any change might apply to different treatments we included both patients given 3+7 (or 3+7-like regimens) on SWOG studies and patients given high-dose ara-C-containing regimens at MD Anderson Cancer Center (MDA).

Patients and Methods

Analyses included 1,409 SWOG patients on nine trials between 1991 and 2009 and 1,942 patients treated on various trials at MDA between 1991 and 2009. Seven hundred and sixty-nine of the SWOG patients received 3+7 alone and are analyzed separately below; in the earlier years of the 1991-2009 period the daily daunorubicin dose was typically 45mg/m^2 , while it was 60 mg/m^2 in later years. Another 273 received 3+7 + gemtuzumab ozogamicin (with 45 mg/m^2 daunorubicin). Two hundred received regimens of similar intensity as 3+7 (mitoxantrone + etoposide +/- PSC 833), while a final 167 were given daunorubicin + ara-C at 2-3g/m^2 daily +/- cyclosporine. 92% of the 1,942 MDA patients received ara-C at 1.5- 2.0 g/m^2 daily × 3-5 days, together with idarubicin (IA), fludarabine (FA, FLAG, FLAG+ida), topotecan, troxacitabine, or clofarabine with or without non-cytotoxic agents such as tipifarnib, vorinostat, or sorafenib. Institutional review boards of participating institutions approved all protocols, and patients were treated according to the Declaration of Helsinki.

Statistical Analysis

TRM was defined as death within 28 days after initiation of induction therapy, based on findings that weekly TRM rates declined sharply once 4 weeks had elapsed from initiation of therapy, suggesting that the first 4 weeks of therapy was a distinct time (2). TRM rates were estimated and exact binomial confidence intervals were calculated. Univariate associations of TRM with categorical variables were assessed using Fisher's exact test and associations with quantitative variables were assessed using the Kruskal-Wallis test. Logistic regression was used to assess multivariate associations with TRM. The covariates considered in these analyses were those previously found independently associated with TRM (2): age, WBC, platelet count, % blood blasts (each considered as numerical variables), performance status (ECOG 0-1 vs. >1), and de novo vs. secondary AML. Criteria for secondary AML were therapy-related AML and/or an antecedent hematologic disorder (AHD). MDA patients were considered to have an AHD given a documented abnormality in blood count for > 1 month before diagnosis of AML while an AHD in SWOG required a marrow showing MDS. Trend tests were done to test the hypothesis that there was no tendency for a decline in TRM over time (year categories were 1991-1995, 1996-2000, 2001-2005, and 2006-2009).

Results: Early death in the SWOG and MDA cohorts

Table 1 (p17) summarizes patient characteristics over four time periods between 1991 and 2009. In both the SWOG and MDA cohorts, median age decreased over time. Correspondingly, the proportion of patients with PS of 0 or 1 increased with 60-70% of patients in 1991-1995 having PS of 0 or 1 increasing to more than 85% during 2006-2009. In the SWOG cohort, no patients treated between 2006 and 2009 had secondary AML, such patients being ineligible for the trial open during this period. The MDA cohort included more patients with secondary AML than did the SWOG cohort, reflecting the differences in criteria for AHD noted above. Of most interest, in both SWOG and MDA TRM rates declined over time ($p<0.001$), from 18% and 16% during 1991-1995 to 3% and 4% during 2006-2009.

Table 2 (p18) summarizes the relations between patient characteristics and TRM. Patients with TRM were older (median 67 versus 56 in SWOG and 66 versus 58 at MDA both $p<0.001$), had higher pre-treatment WBC counts (median 24,000 versus 13,000 and 15,000 versus 6,000, $p=0.005$ and $p <0.001$), and lower platelets counts (46,000 versus 55,000 and 36,000 versus 50, 000, $p=0.01$ and $p <0.001$). Twenty-three percent of SWOG patients with PS >1 had TRM compared to 8% of patients with PS 0-1; corresponding rates were 26% and 4% at MDA (both $p< 0.001$). Despite the different definitions of secondary AML, TRM was more frequent in such patients both in SWOG ($p<0.001$) and at MDA. ($p=0.011$).

To clarify whether the decline in TRM (Table 1) merely reflected the higher proportion of patients with covariates associated with decreased TRM (Table 2), multivariate regression analyses were done to assess changes in TRM rates over time while adjusting for these covariates (Tables 3 (p19) and 4 (p20) and 5 (p21)). Because SWOG had no patients with secondary AML (associated with TRM) during the low TRM 2006-2009 period, two

regression analyses were performed: one including secondary AML as a covariate and a second excluding all patients with secondary AML (Tables 3 and 4). When including secondary AML as a covariate, there was no evidence of change in TRM rates over time (trend p=0.14). When patients with secondary AML were excluded (13% of all the 1409 SWOG patients), there was evidence of a decrease in TRM rates over time (trend p=0.003). Results for the MDA analysis are presented in Table 5 (p21) and there was evidence that TRM rates decreased over time (trend p=0.001).

To evaluate whether there was evidence that changes in TRM rates over time were covariate specific, we evaluated interaction between time and the covariates of the multivariate models. None of the interaction terms were significant. Additionally, an analysis limited to patients age 60 or younger and including the same covariates noted above found a decrease over time (p = 0.018 at MDA , p = 0.12 in SWOG and p = 0.031 in SWOG excluding the patients with secondary AML).

TRM in SWOG patients who received 3+7

The same analyses as above were performed in the subset of SWOG patients who received 7+3 therapy without other agents (n= 769). The TRM rate was 11%, with rates of 18%, 12%, 13%, and 1% in the four time periods. The covariates associated with TRM were those so associated in the full cohort. In multivariate analysis when secondary AML was included there was not a significant change in TRM rates over time (trend p=0.12), but when patients with secondary AML were excluded from the analysis, the decrease was significant (trend p=0.05).

Discussion

Our results indicate that TRM rates after receipt of AML induction have fallen over the 1991-2009 period, with the most dramatic decrease in the final four of these years. The same trend occurred in both SWOG, where the predominant induction therapy was 3+7, and at MDA, where most patients received “more intense” induction, in particular containing ara-C at 1.5- 2.0g/m^2 daily × 3 -5 days.

Several issues merit attention. Perhaps first is whether death occurring within the initial 28 days after start of induction is a plausible criterion for TRM. Although any criterion might appear arbitrary, 28 days seems supported empirically. In particular, weekly death rates, at least in SWOG and at MDA, appeared high and constant during weeks 1-4 after the start of therapy after which they declined precipitously in both younger and older patients (2). Furthermore, covariates associated with death during days 1-28 were not those associated with failure to enter CR despite surviving these 28 days or with relapse (2,11). This suggested that these 4 weeks were a distinct period with patients dying during this time a distinct group. The same conclusion was reached in an MDA analysis based on patients treated during the 1980s (3). Similar results to those presented here can be found when defining TRM as death within 60 days after the start of induction; in SWOG rates decreased over the time periods analyzed here from 27%, 22%, 20%, to 6%, with similar trends in MDA: 25%, 22%, 15%, 8%.

A great variety of induction regimens were used during the 18 years encompassed in these analyses. In particular, MDA patients generally received much higher doses of ara C than did SWOG patients. While such heterogeneity might be viewed as a weakness, the similar declines in TRM at MDA and in de novo SWOG patients (who constituted 87% of those treated in SWOG) might also be viewed as strengthening the case that our results can be generalized. The same is true considering the similarity in results in SWOG patients given 3+7 versus other regimens. Likewise, while the daunorubicin doses used in SWOG trials varied with time, in general higher doses were used in later years, which, other things being equal, might have been expected to increase the TRM rate but did not.

A fundamental issue is whether decreasing TRM rates are due to a true effect of time rather than an effect of the seemingly better prognoses of patients treated in the more recent periods. The factors contributing to these better prognoses comprise those that are known (such as younger age, better performance status, and de novo rather than secondary AML) and those that cannot be known (for example selection bias as discussed below). We used multivariate analyses to account for the known covariates. It should be noted that during 2006-2009 when TRM rates in SWOG were lowest (3%), no SWOG patients had secondary AML. Hence multivariate analysis cannot distinguish between an effect of time and an effect of absence of secondary AML. Although the number of secondary AML patients in SWOG in earlier periods was relatively small, this confounding presumably accounted for the p-value of 0.17 when testing the hypothesis that there had been no successive decrease in TRM over the time periods. The small number of secondary AML patients also hampered efforts to examine whether the effect of secondary AML on TRM had declined during the first three of these periods. These problems led us to do a separate analysis limited to SWOG patients with de novo AML, who accounted for 87% of SWOG patients from 1991-2009. This analysis (Table 4) rejected with p=0.003 the hypothesis that there had been no decrease in TRM during the periods examined. A similar conclusion was reached using MDA data, which included more patients with secondary AML, although this increase reflected to some extent different definitions of secondary AML in SWOG and at MDA.

There could be unknown covariates that could have contributed to our findings. In particular, the decrease in patient age over time, especially in SWOG, raises the possibility that in later years older patients preferentially received less intense regimens, which became increasingly available in these years. In fact, the decrease in age of SWOG patients during the most recent years was because there was no protocol active for older patients. It is, nonetheless, plausible that the older patients included in the later years of our study were more favorable than those included in the earlier years, a possible selection bias that cannot be addressed by multivariate analyses. However we found no evidence that the decline in TRM was limited to older patients. In fact, a subset analysis of patients age 60 and younger had the same results as the primary analysis including all ages. And while it is reasonable to assume a tendency over time to give older patients less intense regimens, it is less reasonable to assume the same for younger (e.g., under age 60 or 65) patients. Similarly, although our ability to detect these was limited, the absence of statistical interactions between a decrease in TRM and performance status or WBC suggests that our findings are applicable to patients with better performance status and patients with high WBC, with both of these groups unlikely to have received less intense therapy in the later years of this study.

Of course randomization, the best way to address selection bias, is not applicable in our patients.

Furthermore, a decline such as we observed in TRM rate in patients given intense regimens is certainly quite plausible given the introduction of newer antibiotics and antifungals, in particular azoles and echinocandins effective against molds (12-15). It is highly likely that the same factors underlie the decrease in non -relapse mortality seen following HCT (10).

Regardless of the explanations, the decline in TRM after induction therapy with 3+7 (SWOG) or more intense regimens (MDA) has important implications. Recent years have seen the introduction of drugs such as azacitidine and decitabine. Although these agents have less anti AML activity than more intense regimens, a good part of their appeal is that they are likely to have a lower 28 day TRM rate. However, although we cannot be sure our observations extend beyond patients eligible for intensive regimens at SWOG institutions or MDA, our results suggest that TRM is not the problem it once was.

References

1. Appelbaum F, Gundacker H, Head D, Slovak M, Willman C, Godwin J, et al. Age and acute myeloid leukemia. Blood. 2006; 107:3481–3485. [PubMed: 16455952]
2. Walter R, Othus M, Borthakur G, Ravandi F, Cortes J, Pierce S, et al. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. J Clin Oncol. 2011; 29:4417–4423. [PubMed: 21969499]
3. Estey E, Smith TL, Keating MJ, McCredie KB, Gehan EA, Freireich EJ. Prediction of survival during induction therapy in patients with newly diagnosed acute myeloblastic leukemia. Leukemia. 1989; 3:257–63. [PubMed: 2927176]
4. Burnett AK, Milligan D, Prentice AG, Goldstone AH, McMullin MF, Hills RK, Wheatley K. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. Cancer. 2007; 109:1114–24. [PubMed: 17315155]
5. Fenaux P, Mufti G, Hellström-Lindberg E, Santini V, Gattermann N, Germing U, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol. 2010; 28:562–569. [PubMed: 20026804]
6. Platzbecker U, Germing U. Combination of azacitidine and lenalidomide in myelodysplastic syndromes or acute myeloid Leukemia—a wise liaison? Leukemia. 2013 in press.
7. Pollyea D, Kohrt H, Gallegos L, et al. Safety, Efficacy and biological predictors of response to sequential azacitidine and lenalidomide for elderly patients with acute myeloid leukemia. Leukemia. 2011; 26:893–901. [PubMed: 22033493]
8. Kantarjian H, Thomas X, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol. 2012; 30:2670–2677. [PubMed: 22689805]
9. Quintas-Cardama A, Santos F, Garcia-Manero G. Histone deacetylase inhibitors for the treatment of myelodysplastic syndrome and acute myeloid leukemia. Leukemia. 2010; 25:226–235. [PubMed: 21116282]
10. Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorror ML, Boeckh M, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med. 2010; 363:2091–2101. [PubMed: 21105791]
11. Walter R, Othus M, Borthakur G, Ravandi F, Cortes J, Pierce S, et al. Quantitative effect of age in predicting empirically-defined treatment-related mortality and resistance in newly diagnosed

AML: case against age alone as primary determinant of treatment assignment. Blood. 2010; 116:2191. ASH abstract # 2191.

12. Baden L. Prevention and therapy of fungal infections in bone marrow transplantation. Leukemia. 2003; 17:1038–1041. [PubMed: 12764365]
13. Aperis G, Alivanis P. Posaconazole: a new antifungal weapon. Rev Recent Clin Trials. 2011; 3:204–19. [PubMed: 21682687]
14. Pagano L, Caira M, Candoni A, Aversa F, Castagnola C, Caramatti C, et al. for the SEIFEM Group. Evaluation of the practice of antifungal prophylaxis use in patients with newly diagnosed acute myeloid leukemia: results from the SEIFEM 2010-B Registry. Clin Infect Dis. 2012; 55:1515–1521. [PubMed: 22955439]
15. Walsh T, Teppler H, Donowitz G, Maertens J, Baden L, Dmoszynska A, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med. 2004; 351:1391–1402. [PubMed: 15459300]

Table 1

Distribution of patient characteristics over time. Median (min, max) or % reported.

Characteristic	Cohort	1991-1995	1996-2000	2001-2005	2006-2009	P-value
N	**SWOG**	392	406	113	498	
	MDA	102	638	732	470	
Age	**SWOG**	64 (17, 89)	65 (19, 85)	58 (20, 83)	49 (19, 60)	<0.001
	MDA	58 (18, 83)	60 (17, 87)	59 (14, 85)	56 (18, 88)	<0.001
WBC ($\times 10^3$)	**SWOG**	18 (0, 416)	13 (1, 244)	10 (1, 370)	13 (0, 545)	0.16
	MDA	14 (0, 262)	8 (0, 394)	7 (0, 433)	5 (0, 204)	<0.001
Platelets ($\times 10^3$)	**SWOG**	56 (3, 537)	53 (2, 1200)	49 (5, 1200)	55 (2, 9300)	0.39
	MDA	59 (5, 1355)	46 (3, 2292)	51 (4, 676)	45 (4, 535)	0.02
Blood blast %	**SWOG**	32 (0, 99)	30 (0, 99)	22 (0, 97)	31 (0, 99)	0.044
	MDA	24 (0, 94)	20 (0, 99)	18 (0, 99)	17 (0, 98)	0.28
PS 0/1 %	**SWOG**	69	84	81	87	<0.001
	MDA	60	65	80	86	<0.001
De novo AML %	**SWOG**	80	78	85	100	<0.001
	MDA	50	52	45	55	0.007
TRM %	**SWOG**	18	13	12	3	<0.001
	MDA	16	14	9	4	<0.001

Leukemia. Author manuscript; available in PMC 2015 June 05.

Table 2

Univariate associations between TRM and patient characteristics. Median (min, max) or % reported.

Characteristic	Cohort	TRM	No TRM	P-value
N	**SWOG**	153	1256	
	MDA	186	1756	
Age	**SWOG**	67 (23, 89)	56 (17, 87)	<0.001
	MDA	66 (18, 84)	58 (14, 88)	<0.001
WBC ($\times 10^3$)	**SWOG**	24 (0, 320)	13 (0, 545)	0.0049
	MDA	15 (0, 394)	6 (0, 433)	<0.001
Platelets ($\times 10^3$)	**SWOG**	46 (5, 684)	55 (2, 9300)	0.0095
	MDA	36 (4, 395)	50 (3, 2292)	<0.001
Blood blast %	**SWOG**	36 (0, 99)	30 (0, 99)	0.073
	MDA	24 (0, 99)	18 (0, 99)	0.032
PS 0/1 vs >1	**SWOG**	8% vs 23%	92% vs 77%	<0.001
	MDA	4% vs 26%	96% vs 74%	<0.001
De novo vs Secondary	**SWOG**	9% vs 27%	91% vs 72%	<0.001
	MDA	8% vs 11%	92% vs 89%	0.011

Table 3

ED regression results for SWOG cohort

	OR	95% CI	P-value
Age (per year)	1.06	(1.03, 1.09)	<0.001
PS 2+ (ref PS 0-1)	2.47	(1.64, 3.72)	<0.001
WBC (per 1000)	1	(1, 1.01)	0.096
Platelets (per 1000)	1	(1, 1)	0.29
Blood blasts (per 1%)	1	(1, 1.01)	0.27
Secondary AML (ref de novo)	2.06	(1.29, 3.29)	0.003
1996-2000 (ref 1991-1995)	0.75	(0.48, 1.18)	0.21
2001-2005 (ref 1991-1995)	0.81	(0.40, 1.62)	0.55
2006-2009 (ref 1991-1995)	0.59	(0.28, 1.24)	0.16

Table 4

ED regression results for SWOG cohort excluding patients with secondary AML

	OR	95% CI	P-value
Age (per year)	1.05	(1.03, 1.06)	<0.001
PS 2+ (ref PS 0-1)	2.40	(1.56, 3.70)	<0.001
WBC (per 1000)	1	(1, 1.01)	0.017
Platelets (per 1000)	1	(0.99, 1)	0.18
Blood blasts (per 1%)	1	(1, 1.01)	0.31
1996-2000 (ref 1991-1995)	0.68	(0.42, 1.09)	0.11
2001-2005 (ref 1991-1995)	0.46	(0.19, 1.13)	0.09
2006-2009 (ref 1991-1995)	0.41	(0.22, 0.78)	0.006

Table 5

ED regression results for MDA cohort

	OR	95% CI	P-value
Age (per year)	1.03	(1.01, 1.04)	<0.001
PS 2+ (ref PS 0-1)	5.75	(4.03, 8.21)	<0.001
WBC (per 1000)	1.01	(1, 1.01)	<0.001
Platelets (per 1000)	0.99	(0.99, 1)	<0.001
Blood blasts (per 1%)	0.99	(0.99, 1)	0.088
Secondary AML (ref de novo)	1.53	(1.07, 2.18)	0.019
1996-2000(ref 1991-1995)	0.89	(0.47, 1.69)	0.72
2001-2005(ref 1991-1995)	0.70	(0.37, 1.36)	0.29
2006-2009(ref 1991-1995)	0.36	(0.16, 0.78)	0.01