Research paper

The relationship between clinical trial accrual volume and outcomes in acute myeloid leukemia: A SWOG/ECOG-ACRIN study (S0106 and E1900)

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ARTICLE INFO

ABSTRACT

Purpose: To study whether institutional clinical trial accrual volume affects clinical outcomes of younger (age less than 61 years) patients with acute myeloid leukemia.

Patients and methods: We investigated the impact of clinical trial accrual on response rates, early mortality and survival in patients with AML enrolled between 2002 and 2009 into two parallel cooperative group clinical trials SWOG S0106/ECOG-ACRIN E1900. Institutions were classified as low- (LAIs) ($\leq$ 9 enrolled patients) or high-accruing institutions (HAIs) ($\geq$ 10 enrolled patients). Fisher's exact text and logistic regression analysis were used to analyze the response and early mortality rates. The effect of accrual volume on survival was analyzed by log-rank tests and Cox regression models.

Results: A total of 1252 patients from 152 institutions were included in the final analyses. The median clinical trial registrations in HAIs was 19 patients (range, 10 to 92) versus 3 (range, 1 to 9) patients in LAIs. In multivariate analyses, HAIs, as a quantitative covariate, was associated with improved complete remission rates (odds ratio (OR) 1.08, p = 0.0051), but no improvement median overall survival (HR 0.97, p = 0.065) or median event-free (hazard ratio (HR) 0.97, p = 0.05). Early mortality rates were similar between cohorts and academic affiliation had no impact on response rates or survival.

Conclusion: Clinical trial accrual volume, had an independent, albeit modest, impact on complete remission rates, but not on overall survival and event-free in younger patients with AML.

1. Introduction

The correlation between increased hospital volume and improved outcomes is a remarkably consistent observation in studies of surgical specialties, including operations and interventional procedures, and nonsurgical hospital-based care, such as treatment of congestive heart failure, mechanical ventilation, and intensive care [1–4]. In oncology, similar volume-outcome correlations have been reported in patients with head and neck and lung cancer in addition to patients undergoing allogeneic stem cell transplant (alloHCT) for chronic myeloid leukemia [5–7]. In patients with acute myeloid leukemia (AML), only limited data are available showing that high volume hospitals observed lower mortality rates following inpatient chemotherapy compared to low volume hospitals [8]. This study, however, was limited by

heterogeneous cohorts of patients, lack of information regarding chemotherapy regimen used or stage of the disease being treated (induction versus consolidation or in remission versus relapsed/refractory) and absence of critical prognostic factors in AML, such as baseline white blood cell and platelet count, performance status at diagnosis and cytogenetic information.

Principles of good clinical practices are critical requirements to the conduct of research involving human subjects and were developed to ensure that study subjects receive safe, high-quality, protocol-driven care from highly trained research personnel overseen by experienced and well-informed investigators. The same elements required for cancer centers to participate in clinical research protocols could also translate into beneficial changes in the hospital environment that affects outcomes of care for patients treated outside the trial setting [9–11]. Therefore, it is possible that institutional clinical trial accrual could, at least partially, serve as a surrogate for clinical expertise and impact short- and long-term outcomes in AML. In fact, these effects may be particular relevant in patients with AML where clinical trial accrual rates routinely exceed accrual rates observed in solid tumor clinical trials and patients are frequently cared in academic centers with emphasis on clinical research [12,13].

To address the effect of hospital volume on outcomes in a well-defined and homogenous cohort of AML patients, we examined whether institutional clinical trial accrual volume, used as a surrogate for institutional experience, was associated with induction mortality or survival for younger (≤ 60 years) patients with previously untreated AML enrolled onto two prospective, multicenter, randomized controlled trials conducted by SWOG (formerly known as Southwest Oncology Group) and Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN).

2. Methods

2.1. Study design and selection of datasets

We analyzed individual patient data from two randomized controlled trials activated by the National Cancer Institute cooperative group trials to adult patients with AML between December 2002 and August 2009. These results of these studies have been described [14–17]. In brief, patients had AML according to the World Health Organization criterion ($\geq 20\%$ blasts), aged 17 to 60 years, with adequate performance status and organ function. Patients with acute promyelocytic leukemia (M3 AML) were not eligible. All patients provided written informed consent in accordance with local policies, federal regulations, and the Declaration of Helsinki. These trials were registered with www.clinicaltrials.gov as #NCT00085709 and NCT00049517.

2.2. Study design and treatment groups

2.2.1. ECOG-ACRIN 1900

Patients with untreated AML were randomized to receive either 45 mg/m^2 or 90 mg/m^2 of intravenous daunorubicin daily for 3 days, together with intravenous cytarabine (100 mg per square meter per day) continuously for 7 days from December 2002 through November 2008. A second induction course with daunorubicin 45 mg/m^2 could be given for persistent disease. Post-remission therapy options included alloHCT or autologous stem-cell transplantation following two cycles of high-dose cytarabine therapy, based on the risk of relapse. Patients who underwent autologous stem-cell transplantation were randomized to receive a single dose of gemtuzumab ozogamicin prior to transplant. Inclusion of patients with a history of an antecedent hematologic disorder within 6 months of AML diagnosis was permitted.

2.2.2. SWOG S0106

Between August 2004 through August 2009, patients were randomized between 2 induction regimens: either DA (daunorubicin 45 mg/m^2 days 1–3 plus cytarabine 100 mg/m^2 days 1–7) plus GO (gemtuzumab ozogamicin 6 mg/m^2 on day 4); or DA (daunorubicin 60 mg/m^2 days 1–3 plus cytarabine 100 mg/m^2 on days 1–7). A second course using the DA regimen was allowed for patients with residual AML. Post-remission therapy for patients in remission included 3 courses of consolidation therapy with cytarabine 3 g/m^2 every 12 h on days 1, 3, and 5. After consolidation therapy, patients were randomized between GO (5 mg/m^2, 3 doses at least 28 days apart) vs observation. Patients with AML arising from a prior hematological malignancy were ineligible for this study.

2.3. Treatment outcomes

Complete remission (CR) was defined according to the International Working Group Guidelines [18]. Early mortality (EM) was defined as death within 28 days of initiating therapy [19]. Event-free survival (EFS) was measured from date of randomization to the first of date of protocol therapy without a CR, relapse from CR, or death from any cause, with observations censored at the day of last contact for patients last known to be alive without report of relapse. Overall survival (OS) was measured for all patients from the day of initial randomization until death from any cause, with censoring at the day of last contact for patients last known to be alive. Relapse-free survival (RFS) was measured for patients who achieved CR from the date of CR until the first of relapse or death from any cause, with observations censored at the day of last contact for patients last known to be alive without report of relapse.

2.4. Statistical considerations

Our primary objective was to analyze the association between institutional accrual volume and outcomes. As a surrogate for institutional expertise, we used institutional accrual volume to two recent AML clinical trials conducted by SWOG and ECOG-ACRIN during the 7-year period. Data were collected and evaluated according to the standard practices of SWOG and ECOG-ACRIN. Median institutional accrual to S0106 was used to define the separate accrual categories: institutions that registered 10 or more eligible patients were denoted hereafter High Accruing Institutions (HAIs) and institutions that registered 9 or fewer eligible patients were denoted Low Accruing Institutions (LAIs). Hospital volume was analyzed quantitatively (number of eligible patients registered to the trial from same institution) and as a binary covariate (10 or more patients versus 9 or fewer patients). To avoid confounding of outcomes by study and treatment arm, analyses were stratified by study (SWOG versus ECOG-ACRIN) and treatment arm. Fisher's exact text and logistic regression analysis were used to analyze the effects of treatment group and other covariates on CR rates and early death. Log-rank tests and Cox regression were used to analyze OS, RFS, and EFS. Academic affiliation was defined as those institutions with Accreditation Council for Graduate Medical Education (ACGME) training programs for hematology and/or medical oncology.

3. Results

3.1. Study population and comparison between SWOG and ECOG trials

There were 1252 patients included in the following analyses. Patients treated in the SWOG trial had higher CR rates (70% versus 65%, p = 0.05). In addition, longer median OS (47 months versus 21 months, p < 0.0001) was observed for patients treated on the SWOG trial. These differences remained significant when patients with secondary AML (n = 22) enrolled on the ECOG-ACRIN trial were excluded from the analysis (p < 0.001). A histogram depicting institutional volume is presented on Supplemental Fig. 1. Among the 152 institutions participating on these studies, a total of 846 (68%) patients (median of

Table 1
Patient and Tumor Characteristics by Accrual Volume.

Variable	LAIs (n = 406)	HAIs (n = 846)	*p*-value
Age (median, range)	47 (18,61)	48 (17,61)	0.36
WBC at diagnosis (x 10^9/L, range)	11 (0,370)	12 (0,545)	0.06
Bone Marrow Blasts (% median, range)	64 (3,100)	65 (3,100)	0.25
Female (N, %)	179 (44)	425 (50)	0.046
ECOG Performance Status (N, %)			
0-1	357 (88)	772 (92)	0.16
2-3	47 (12)	69 (8)	
Response to Induction Chemotherapy (N, %)			
Complete Remission	266 (66)	575 (68)	0.24
Early Mortality	15 (4%)	25 (3%)	0.42
Institution Affiliation (N, %)			
Non-academic	266 (66)	274 (32)	< 0.01
Academic	140 (34)	572 (68)	
Cytogenetic risk (NCCN)			
Favorable	52 (13)	114 (13)	0.12
Intermediate	161 (41)	285 (34)	
Unfavorable	73 (18)	176 (21)	
Missing	116 (29)	271 (32)	

Footnotes: LAIs – Low Accruing Institutions, HAIs – High Accruing Institutions, WBC – White blood cell count, ECOG – Eastern Oncology Group.

19 patients (range, 10 to 92) were registered by the 34 (22%) HAIs. LAIs (n = 118) registered a median of 3 (range, 1 to 9) patients on trial. Differences in the distribution of HAIs were observed in patients enrolled in the two clinical trials. For the ECOG-ACRIN E1900 clinical trial, approximately 40% of all patients registered were enrolled in one of four institutions. The four highest accruing institutions in the SWOG-led S0106 trial enrolled only 20% of all patients. Patients at HAIs were more commonly males and registered at academic centers. Time to initiation of therapy was similar between HAIs and LAIs (p = 0.23). Other baseline characteristics for subjects included in our analyses are summarized in Table 1.

3.2. Early mortality and treatment efficacy

Early mortality (EM) rates were not significantly different between HAIs and LAIs (4% versus 3%, p = 0.42). On multivariable analysis, neither the binary nor the quantitative institutional volume covariates were associated with EM rates. In addition, CR rates were not significantly different between HAIs and LAIs (68% versus 66%, p = 0.24). However, in a multivariable logistic regression model, higher accrual volume with institution volume as a quantitative covariate was independently associated with improvement in CR rates (odds ratio (OR) 1.08 (95% confidence interval (CI) 1.02, 1.14), p = 0.0051). (Table 1)

3.3. Survival analyses

With a median follow-up of 5.6 years among censored patients, patients treated in HAIs had improvement in the overall survival (median 2.4 years for HAIs versus 2.0 years for LAIs, p = 0.043) (Fig. 1). No differences in event-free survival (p = 0.098) or relapse-free survival (p = 0.18) were observed between HAIs and LAIs (Supplemental Fig. 2). Using institution volume as a quantitative covariate, in Cox regression models favorable and unfavorable karyotype and worse performance status at registration are associated with event-free survival (EFS). Treatment in HAIs (HR 0.97 (95% CI 0.95, 1), p = 0.05) was not independently associated with EFS (Table 2). Treatment at HAIs was not independently associated with relapse-free survival (HR 0.98 (95% CI 0.95, 1.02), p = 0.42) (data not shown) or overall survival (HR 0.97 (95% CI 0.94, 1.0), p = 0.069).

Overall survival
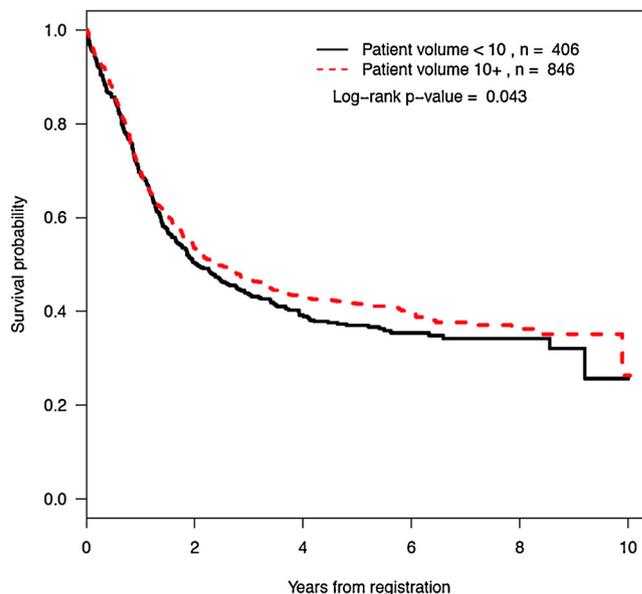
Fig. 1. Kaplan-Meier estimates by accrual volume of overall survival.

Table 2
Cox regression model for overall survival and event free survival using institutional volume as quantitative covariate.

Covariate	HR (95% CI)	p-value
Overall Survival (n = 1214)		
Institutional Volume (per 10 patients)	0.97 (0.94, 1)	0.069
Age (years)	1.02 (1.01, 1.02)	< 0.01
WBC (x 10^3)	1.18 (1.02, 1.36)	0.022
Bone Marrow Blasts (10%)	1.03 (1., 1.06)	0.063
Platelets (x 10^3)	1.01 (0.99, 1.03)	0.25
Male gender (ref = female)	1.1 (0.95, 1.27)	0.21
PS 2-4 (ref = PS 0-1)	1.61 (1.27, 2.04)	< 0.01
Favorable risk (ref = intermediate)	0.53 (0.4, 07)	< 0.001
Unfavorable risk(ref = intermediate)	1.9 (1.57, 2.3)	< 0.001
Missing cytogenetic information	0.95 (0.8, 1.15)	0.62
Event-Free Survival (n = 1212)		
Institutional Volume (per 10 patients)	0.97 (0.95, 1)	0.05
Age (years)	1.01 (1, 1.01)	0.1
WBC (x 10^3)	1.08 (0.94, 1.24)	0.26
Bone Marrow Blasts (10%)	1.02 (0.99, 1.05)	0.25
Platelets (x 10^3)	1.0 (0.99, 1.02)	0.61
Male gender (ref = female)	1.07 (0.93, 1.22)	0.33
PS 2-4 (ref = PS 0-1)	1.3 (1.04, 1.63)	0.02
Favorable risk (ref = intermediate)	0.55 (0.43–0.71)	< 0.001
Unfavorable risk(ref = intermediate)	1.48 (1.24, 1.77)	< 0.001
Missing cytogenetic information	1 (0.85, 1.04)	0.97

Abbreviations: ref – reference.

3.4. Impact of treatment on academic institutions

A greater proportion of patients in the high-volume category were treated at academic institutions (68% versus 34%, p < 0.001). However, no significant differences in CR rate (p = 0.36), EFS (p = 0.081), RFS (p = 0.084), or OS (p = 0.74) were observed between subjects treated at academic versus non-academic institutions. Type of institution (academic versus non-academic) was also not significantly associated with any of these outcomes on multivariable analysis and there were no significant interactions between type of institution and quantitative and non-quantitative volume (summaries not shown).

4. Discussion

In an analysis of two recent US Intergroup AML clinical trials, we observed modest associations between trial accrual volume and CR rates, but no improvement in OS or EFS. Our observations add to evidence demonstrating that experienced care teams likely execute superior treatment plans that translated into an improvement in remission rates, the most intense treatment period in AML induction therapy. Interestingly, early death rates were similar between cohorts. Because academic institutions were significantly more likely to be in the high-volume category, we hypothesized that differences in academic affiliation could explain the discrepancies between in clinical outcomes. Our results failed to demonstrate an association between type of institution and CR, EFS or OS.

Unfortunately, cooperative group sponsored clinical trials in AML do not adequately collect data on type and timing of alloHCT or salvage therapies following relapse. Thus, we cannot evaluate whether treatment in HAIs had an impact on referral to alloHCT, the potential timing of potential transplants or whether alloHCT influenced outcomes for patients included in these analyses. This information is of particular interest in these cohorts given that survival was similar between HAIs and LAIs up to 12 months post randomization. These observations suggest that late relapses or deaths (such as transplant related mortality) may have negatively impacted outcomes in LAIs. In addition, location of post-remission treatment cycles is not captured adequately and it may also impact our observations.

Despite extensive data demonstrating a strong correlation between institutional or procedure volume and improved clinical outcomes in solid-tumors and non-malignant conditions, only limited data have been reported in patients undergoing intensive therapy for AML [20]. Our results, demonstrating improved CR rates add modestly to a report demonstrating a positive correlation between decreased mortality in institutions treating a higher volume of patients with AML [8]. In addition, our observations validate and extend the recommendations from British Authorities stipulating that AML patients only receive therapy at specialized institutions treating a minimum of 5 patients per year with intensive chemotherapy [21].

Our collaborative effort among the leukemia committees of two separate cooperative groups has significant strengths. Our observations result from analyses performed in a homogenous cohort of AML patients that were uniformly treated during a similar time period both at academic and community practices. This novel initiative has rarely been utilized in AML clinical trials and it expanded on the sample size analyzed. However, clear justifications for the improved CR rates observed with higher-accruing institutions remain unclear. First, accrual volume was not associated with RFS, suggesting increased relapse rate is unlikely the cause of worse outcomes. It is possible that better salvage strategies are available in institutions that accrue more patients to such trials. Of interest are the observations that outcomes following alloHCT are influenced by institution volume and partially affected by the experience of the care team [7,22].

We cannot entirely exclude a possible contribution of referral bias leading to differences in patients treated at HAIs versus LAIs and hence differences in the reported outcomes. However, we observed no differences in the demographics of patients registered in HAIs versus LAIs, except for the association between HAIs mostly being academic institutions. In addition, we did not find any interactions between institution affiliation and outcomes between institutional category. Finally, participation in these clinical trials may not be a surrogate for clinical expertise in AML [23] as accrual to intergroup trials may not be an indicator of center AML volume. In addition to cooperative group trials, AML patients may be treated off study, on industry sponsored, or on investigator-initiated trials, which may neutralize the impact institutional volume on outcomes for these trials (i.e. institutions may have high volume of AML patients that are not treated in cooperative group trials). In fact, previous studies have shown that AML subjects enrolled into research studies are younger, have better performance status and less comorbidity and lower rates of secondary AML than AML patients excluded from clinical trial participation [24,25].

In conclusion, our data demonstrate the value of collaborative efforts among cooperative groups and suggest strategies to improve research and treatment for patients with AML. Our results suggest that clinical trial enrollment volume is associated with a modest improvement in remission rates, but no effect on event-free survival or overall survival.

Contribution

Drs. Medeiros and Tallman and Drs. Litzow and Erba contributed equally to this article.

Conflict of interest

The authors do not have any conflicts of interest to declare for this manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.leukres.2019.01.007.

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