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Timed sequential therapy for acute myelogenous leukemia: Results of a retrospective study of 301 patients and review of the literature

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Abstract

Timed sequential therapy (TST) aims to improve outcomes in acute myelogenous leukemia (AML) by harnessing drug-induced cell cycle kinetics of AML, where a second drug is timed to coincide with peak leukemia proliferation induced by the first drugs. We analyzed outcomes in 301 newly diagnosed AML patients treated from 2004–2013 with cytarabine, anthracycline, and etoposide TST induction. Median age was 52 (range 20–74) and complete remission rate 68%. With median follow-up 5.8 years, 5-year DFS and overall survival (OS) were 37% (95% CI 31–45%) and 32% (95% CI 27–38%), respectively. In multivariate analysis, older age, unfavorable cytogenetics, and WBC $> 50 \times 10^9/L$ resulted in worse OS. Among patients not undergoing blood and marrow transplant, a propensity score analysis, which reduces imbalance in baseline characteristics, showed consolidation with TST compared with 1 or more cycles high-dose cytarabine trended toward lower DFS and post-remission survival with hazard ratio (HR) 1.9 (95% CI 0.9–4.0), and 1.6 (95% CI 0.7–3.6), respectively. Our results demonstrate the efficacy and feasibility of TST induction for newly diagnosed patients with AML, with results comparable to that seen in clinical trials with other TST therapies and 7 + 3.

Keywords

Timed sequential therapy; Acute myeloid leukemia; Acute myelogenous leukemia; Induction chemotherapy

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Conflicts of interest

The authors declare no conflicts of interest.

1. Introduction

In the late 1960s, attempts to develop induction chemotherapy for acute myeloid leukemia (AML) focused on single agent treatment with cytarabine or anthracyclines, both of which demonstrated *in vitro* activity [1]. The outcomes in these single agent studies showed complete remission (CR) rates of 30–40% for younger treatment-naïve patients [2,3]. Subsequent therapeutic trials demonstrated seven days of cytarabine plus an anthracycline for three days (“7 + 3”) led to improved CR rates to 50–80% [4,5]. Thus, “7 + 3” emerged as the standard of care induction regimen for newly diagnosed patients [4], and has remained such for subsequent decades [5]. Unfortunately, 20–50% of patients remain refractory to induction therapy, and a majority of patients in CR ultimately relapse and die of their disease [6].

There have been diverse attempts to improve induction CR rates, disease-free survival (DFS), and overall survival (OS) for the heterogeneous AML population, including substitution of idarubicin for daunorubicin, [7] dose escalation of anthracyclines [8], addition of etoposide [9], GCSF priming [10], and addition of 6-thioguanine [11]. One biologically rational strategy to improve induction success has been to exploit leukemia cell cycle kinetics by administering a second drug in close approximation to the first drugs at a time when remaining leukemia cells have been recruited into the proliferative cell cycle. The “timed sequential therapy” (TST) pre-clinical and clinical models supported an increased sensitivity to cycle-dependent chemotherapy at the time of drug-induced proliferation [12–16]. Furthermore, two complete courses of TST, with the second course given early in CR at a time of minimal residual disease [17], were modeled as one of the first attempts to cure AML and were shown to be clinically effective resulting in long term disease-free survival in patients [18]. This strategy has been employed successfully in a number of clinical trials [19–21], suggesting that TST induction results in meaningful remission rates and can provide the basis for successful long-term outcomes for patients with AML, whether combined with consolidation chemotherapy or an allogeneic blood and marrow transplant (BMT) as post-remission treatment.

Early TST proof-of-concept studies were performed at Johns Hopkins during the 1970s–1980s [14,22], and TST has remained our institutional cornerstone for AML induction. Here we present the retrospective results of non-trial patients treated with TST-based induction therapy followed by consolidation chemotherapy or BMT.

2. Patients and methods

2.1. Patients

Patients were treated on the inpatient, Burke Adult Leukemia Service at Johns Hopkins Hospital between 2004 and 2013 and received intensive TST. Charts from the leukemia and pharmacy databases were manually reviewed. Patients were nonconsecutive due to prioritization of clinical trials when patients met enrollment criteria and chose to participate. For inclusion in this analysis, patients must have been treated with TST with cytarabine, daunorubicin or idarubicin, and etoposide (AcDVP16 or AcIVP16) for treatment of newly

diagnosed AML. Patients were not excluded based on AML morphology (except acute promyelocytic leukemia), secondary AML, or co-morbidities. AML was diagnosed by review of Wright-stained smears of bone marrow aspirates and biopsies and flow cytometric analyses of cell surface markers, with confirmation by hematopathologists. Chromosomal analysis was routinely obtained and standard AML diagnostics were applied [23]. Availability of molecular markers varied over the time frame of the study but all attempts were made to obtain validated molecular markers, including FLT3-ITD [24]. Cytogenetics were categorized as favorable, intermediate, or unfavorable by the published classification system [25].

2.2. Treatment and evaluation of response

A patient flow diagram is outlined in Fig. 1.

TST induction with AcDVP16 consisted of a 72 h (h) continuous infusion (CI) of cytarabine at a total of 2 g/m² given over days 1–3, a daily 30 min infusion of daunorubicin 45 mg/m² days 1–3, and etoposide 400 mg/m² over 6 h days 8–10. Idarubicin was initially substituted at 12 mg/m² × 3 days during times of daunorubicin shortage; due to concerns of grade 4 mucositis, the dose was decreased within 2 months to 8 mg/m². Patients with WBC $> 50 \times 10^9/L$ or clinical evidence of leukostasis received hydroxurea or a single dose of cyclophosphamide (60 mg/kg) as cytoreduction in advance of AcDVP16, per clinician preference. Consolidation chemotherapy primarily consisted of TST (in the form of AcDAc) or high dose cytarabine (HiDAC). AcDAc consolidation comprised 72 h CI cytarabine 2 g/m² total given over days 1–3 and repeated on days 10–12, with daily 30 min infusion of daunorubicin 45 mg/m² days 1–3. HiDAC consolidation was given per standard dose and schedule [26].

All patients were treated according to the contemporary institutional supportive care practices, similar to a previous trial using TST [19]. Standard AML response criteria were used [27,28]. CR evaluation was typically performed between days 35–60 of induction. Subsequent therapy, including salvage chemotherapy, chemotherapy-based consolidation, or BMT, varied secondary to patient status and clinician preference.

2.3. Statistical analysis

The difference in CR rates in terms of demographic factors and disease characteristics was evaluated with Chi-square and Fisher exact tests for categorical, or Wilcoxon-test for continuous variables. Median follow-up time was calculated based on the reversed Kaplan-Meier method [29]. DFS was calculated as time from CR to relapse or death in CR patients. OS was calculated from the date of TST initiation until death. Post-remission survival (PRS) was defined from date of CR to death to evaluate survival by consolidation therapy within CR patients. All patients alive were censored at last follow-up date. Median survival and 5-year Kaplan-Meier estimates of survival outcomes after TST treatment or CR were reported. The Cox proportional hazard model was first applied univariately for each baseline characteristic on survival outcomes and proportionality assumption was tested (and found to hold) for all baseline factors. Multivariable analyses were conducted on OS outcome via

backward selection procedure with p-value <0.10 as inclusion criteria. Furthermore, we provided additional OS results of censoring BMT patients at the time of BMT.

Inverse probability of treatment weighting with propensity scores, generated from generalized boosted regression models, were applied for assessing the effect of consolidation treatment (population average treatment effect) of HiDAC versus TST consolidation with AcDAc on DFS and PRS. Propensity scores were used to reduce imbalance in baseline characteristics between the two groups [30] and the propensity scores of the treatment assignment were estimated by including all the baseline variables in Table 1 except induction regimen. All statistical analyses were performed in R3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

Of approximately 714 adults with AML admitted for intensive induction chemotherapy during 2004-2013, 301 (42%) were treated with AcDVP16 or AcIVP16 TST for newly diagnosed AML, with most remaining patients enrolling on clinical trials. All patients in this cohort were deemed fit for intensive chemotherapy by treating providers. Patients who received daunorubicin (n = 284, 94%) versus idarubicin during the period of nationwide daunorubicin shortage (n = 17, 6%) were not different in any of their characteristics (data not shown) and were considered the same for subsequent analyses. Baseline demographics and clinical characteristics for all patients are shown in Table 1. The median age of all 301 patients was 52 years (range, 20-74) and 26% (n = 79) were 60 and above. Only 8% of patients had favorable risk cytogenetics, with the majority (60%) having intermediate, and 31% having unfavorable cytogenetics. Most patients (68%) had *de novo* AML, with the remainder having secondary AML out of MDS (19%), myeloproliferative neoplasms (MPN) or MDS/MPN overlap syndromes (6%), or therapy-related AML (t-AML) (7%).

3.2. Induction therapy

Of 301 newly diagnosed AML patients, 205 (68%) achieved CR following one cycle of TST induction with a median time to recovery of ANC 500/ μ L of 34 days (range, 17–115). Median inpatient hospital stay was 33 days (range, 9–85). Induction mortality, defined as death within 60 days, was 8% with 9 of 25 deaths occurring before day 30. Causes of death were refractory leukemia (n = 9), infection (7), pulmonary failure (3), hemorrhage (3), cardiac arrest (1), and unknown (2). Excluding the 9 deaths from refractory leukemia, the therapy-related induction death rate was 5%. Twelve (5%) of 222 patients <60 years died within 60 days of any cause, compared to 13 (16%) of 79 patients aged 60 and older (p = 0.002). Hematologic and non-hematologic toxicities were not rigorously recorded outside of the trial setting but mucositis, febrile neutropenia, and cytopenias in the Grade 4 range were the most common adverse effects documented.

Of diverse baseline host and disease characteristics, age, cytogenetics, and *de novo* versus secondary AML were significantly associated with response (Table 1). The time frame in

which patients were treated, use of idarubicin versus daunorubicin, gender, presenting WBC, and FLT3-ITD status did not affect the likelihood of achieving CR.

3.3. Relapse and overall survival

Survival statistics are summarized in Table 2 and Fig. 2. With a median follow-up of 5.8 years (range: 8 days to 11.8 years), 5-year OS for all 301 patients was 32% (95% CI 27–38%) and DFS 37% (95% CI 31–45%) within CR patients. Table 3 compares survival statistics from this study and other recent studies using TST and 7 + 3 induction therapy [31–35].

When censored at time of BMT, 5-year OS was 27% (95% CI 20–35%) and DFS 45% (95% CI 36–56%). Older age, unfavorable risk cytogenetics, and secondary leukemia were associated with inferior OS (Fig. 3). Survival was similar between intermediate and favorable-risk cytogenetics ($p = 0.4$), with 5-year OS 38% (95% CI 31–76%) versus 46% (95% CI 28–76%), respectively. FLT3 status was determined in 86% of the cohort and, in patients with known FLT3-ITD, OS did not differ, consistent with results reported previously [36]. DFS was influenced by age ($p = 0.002$), with 5-year DFS 42% (95% CI 35–51%) in patients <60 versus 19% (95% CI 10–36%) 60.

On multivariate analysis, the year of TST treatment (2004–2008 vs 2009–2013), older age per decade increase, high-risk cytogenetics, and WBC $50 \times 10^9/L$ resulted in significantly worse OS (see Supplementary Table 1). Except patient age, no other baseline covariates were significantly associated with DFS.

3.4. Post-remission therapy

Of 205 patients who achieved CR following induction, 90 (44%) received consolidation chemotherapy alone, 98 (48%) underwent BMT at some point during their treatment, and 17 (8%) did not receive any consolidation (Fig. 1). Of the 98 patients who underwent BMT, 41 (42%) went directly after TST induction, 33 (34%) received consolidation HiDAC or AcDAc prior to BMT in CR1, and 24 (24%) received either salvage chemotherapy for relapse ($n = 23$) or an alternate consolidation regimen ($n = 1$) prior to BMT. Of the 90 patients treated with consolidation chemotherapy alone, 59 (66%) received a single cycle of AcDAc, 27 (30%) received one or more cycles of HiDAC, and 4 (4%) received other therapies.

In order to evaluate the impact of consolidation chemotherapy after TST, we studied the outcomes of patients treated with HiDAC ($n = 27$) versus AcDAc ($n = 59$), excluding patients who ultimately underwent BMT. Significantly more patients were treated with AcDAc at our center versus HiDAC before 2009 ($p = 0.01$). Patients treated with HiDAC were younger with a median age of 43 compared to 54 ($p = 0.08$) and were more likely to have favorable risk cytogenetics (30% vs 12%, $p = 0.047$) (Supplementary Table 2). Using the propensity weighting method, consolidation with AcDAc and HiDAC showed a trend towards higher DFS and PRS for patients consolidated with HiDAC, with hazard ratio (HR) 1.9 (95% CI 0.9–4.0, $p = 0.08$) and HR 1.6 (95% CI 0.7–3.6, $p = 0.23$), respectively (Fig. 4). For various reasons (personal choice, co-morbidities, and/or early relapse after confirmed CR) 17 of 205 (8%) patients with CR following initial TST did not proceed with

consolidation therapy. Only four of these patients received further therapy after relapse, with most being treated with best supportive care alone. 5-year PRS and DFS for this group of patients was 13% (95% CI 4–49) and 12% (95% CI 3–43), respectively.

4. Discussion

Increasing the intensity of induction chemotherapy in hopes of improving CR rates and ultimately OS of patients with AML has been the goal of many clinical endeavors in the leukemia community over the past 40 years. Unfortunately, no approach has shown improved remission rates reproducibly beyond those with 7 + 3. Attempts to refine post-remission therapy, including novel approaches to consolidation chemotherapy [37] have made little consistent impact in outcomes for most patients, particularly the elderly [38]. Most improvements have come from increased use of BMT in higher-risk patients and better supportive care [38]. Recently, substantial research focus has shifted to post-BMT maintenance approaches to prolong remissions [39–41]. Nonetheless, patients still require CRs with a sustained response until the immunologic effects of BMT can control the disease. In fact, the depth of CR (amount of residual disease present at time of CR) is a pivotal determinant of post-BMT outcomes [42], and therefore, optimizing induction remains of the utmost importance in AML therapy.

This retrospective study describes our experience utilizing TST as standard induction for a broad spectrum of AML patients. The cohort included adults with conditions that might limit clinical trial eligibility, such as leukostasis, organ dysfunction, and suboptimal performance status. TST resulted in a CR rate of 68%, median OS 17.2 months, and DFS 15 months, which is similar to what has been reported for 7 + 3 in clinical trial populations (Table 3) [31–34]. It is noteworthy that these outcomes were obtained with intermediate anthracycline dosing (total induction daunorubicin 135mg/m² or idarubicin 24–36 mg/m²), minimizing the impact on patients' lifetime cumulative anthracycline dose. Furthermore, the overall induction death rate of 8% in this physiologically diverse patient population compares well to the 5-10% death rate seen in trials using 7 + 3 [8,31]. While performance status and toxicity data were not systematically collected in this retrospective study, toxicities were manageable with aggressive supportive care and antibiotic prophylaxis and we found no evidence of increased toxicity compared to published reports (or our own institutional experience) using 7 + 3 [33,43]. We did, however, observe the time to neutrophil recovery above 500/μL was slightly longer using TST compared to 7 + 3 [33,44,45]. It is notable that with TST, there is no requirement for further chemotherapy based on a day 14 marrow, as with 7 + 3 and “5 + 2.” The addition of 5 + 2 not only leads to the use of additional anthracycline, but delayed count recovery beyond what was seen here [46].

TST was developed to take advantage of the biological properties of the malignant cell population, where a subset of leukemia is quiescent at diagnosis and recruited into the cell cycle by initial doses of chemotherapy. The combination of cytarabine and anthracycline not only debulks the leukemia, but potentially primes resting leukemia cells, sensitizing them to cycle-dependent agents such as etoposide or a second cycle of cytarabine administered days 8–10 [13,47]. In 1980, Vaughan et al. [22] reported on 37 patients with AML who were

treated with TST but no consolidative or additional therapy until relapse. CR was achieved in 56% of cases (65% aged <60), and he later reported prolonged remissions in 44% of patients treated with a second cycle of the same TST, [18,48] suggesting that TST results in deep remissions and can be curative. A later paper by Geller et al. demonstrated prolonged remissions with the use of amsacrine as the second timed sequential drug (i.e. Ac-D-Amsa), further supporting the curative potential of this approach [49].

In the following decade, the TST-based DCTER (daunorubicin, cytarabine, thioguanine, etoposide, and dexamethasone days 1–4 and 10–14) regimen demonstrated a DFS and OS benefit compared to standard chemotherapy, irrespective of post-remission therapy, in pediatric AML [21]. Based on these results, MD Anderson later tested DCTER in adults <50 with non-core-binding factor AML. Despite concerns for increased induction deaths with this intensive regimen, it appeared to improve leukemia-free survival post CR and OS when compared to matched historical controls [35]. Furthermore, the TST platform has been studied in trials internationally by the Acute Leukemia French Association (ALFA) [32,50,51]. ALFA-9000 randomized newly diagnosed adults with AML to TST (daunorubicin, cytarabine d1-3, then mitoxantrone d8-9, cytarabine d8-10), double induction, or 7 + 3 and demonstrated significantly improved disease free survival rates with TST in patients under age 50 [44]. Our results compare favorably to that seen in clinical trial populations with these other TST strategies (Table 3). It is interesting to note that in our cohort well-described poor risk features such as FLT3-ITD and presenting WBC had no impact on CR rate, OS, or DFS. It was encouraging to see that OS and DFS for patients with intermediate-risk cytogenetics did not differ from the outcomes seen with low-risk markers.

Both AcDAc and HiDAC consolidation can result in long-term survival as well as bridges to allogeneic transplant, yet there have been few head to head randomized trials to determine if one strategy is preferable. In our cohort, there was a trend towards improvement in DFS in patients who received HiDAC consolidation compared to a second cycle of TST. A second trend that emerged was that late relapses were seen in TST consolidation patients, which was consistent with data from the ALFA group where patients randomized to consolidation with HiDAC versus TST with mitoxantrone, cytarabine, and etoposide showed a trend toward improved EFS in the HiDAC arm without an effect on OS [51]. Benefits of HiDAC are more clearly demonstrated in patients with favorable-risk cytogenetics, especially core-binding factor AML [52,53]. One explanation for HiDAC's success in broader groups of AML patients is that poor-risk patients undergo transplant earlier in their course by using just 1 or 2 courses of HiDAC to bridge them to transplant, and this was the case in our series. It is possible that the long first remissions and eventual late relapses seen with TST consolidation allowed for successful salvage and allogeneic transplant that impacted OS.

There are several limitations to consider with our analyses. First and foremost, this is a retrospective report from a single center that developed the TST model and refined it over many years. Toxicity data, outside of induction-related deaths, were not systematically collected for this large series of patients. Furthermore, understanding the impact of consolidation therapy is limited due to small subgroups, including small numbers of patients with favorable-risk cytogenetics and receiving HiDAC consolidation. Nonetheless, this large series of patients treated with TST induction provides a solid framework of expected

outcomes with this line of therapy in a non-trial population and guides prognostication and therapeutic strategies for new AML patients.

In conclusion, TST offers favorable results in terms of CR rate, OS, and DFS in a non-clinical trial population with manageable toxicities. TST induction can provide long-term survival when followed by consolidation chemotherapy using either HiDAC or AcDAc and TST can provide deep remissions when moving patients to BMT with or without additional chemotherapy. Given the importance of deep remissions leading into BMT, and in light of data suggesting enhanced DFS with TST induction, AcDVP16 remains our preferred upfront approach for younger patients undergoing intensive chemotherapy when clinical trials are not available. Given the lack of increased early deaths or substantial added toxicities, this platform also offers a viable option for testing novel agents [46,54–57]. With the predictable pattern of cell cycle kinetics and recovery, TST particularly lends itself to testing agents that impact diverse aspects of cell cycle progression such as cyclin dependent kinases, DNA repair mechanisms, inflammatory cytokines, and recovery of the immune system.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.leukres.2017.08.009>.

Abbreviations

AcDAc	cytarabine and daunorubicin timed sequential therapy consolidation
AcDVP16	cytarabine daunorubicin and etoposide timed sequential therapy induction
AcIVP16	cytarabine daunorubicin and etoposide timed sequential therapy induction
PRS	post-remission survival
TST	timed sequential therapy

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Fig. 1.
Diagram outlining the flow of newly diagnosed AML patients treated with AcDVP16.

Fig. 2.

Kaplan-Meier curves for overall survival (a) and disease-free survival (b) in newly diagnosed AML patients treated with TST induction. Survival data is presented in Table 2.

Fig. 3. Kaplan-Meier curves for overall survival in newly diagnosed AML patients by age (a), cytogenetics (b), and de novo versus secondary AML (c). P-values correspond to log-rank test. Survival data is presented in Table 2.

Fig. 4. Survival by HiDAc or AcDAc consolidation alone, without eventual BMT. The population average treatment effect (HR) was estimated by Cox proportional hazard model with propensity score weighting method.

Table 1

Baseline characteristics and impact on complete remission rate.

Variables	<i>No. (%) or Median (range)</i>			
	<i>AML patients^a</i>	<i>CR</i>	<i>No CR</i>	<i>p-value</i>
All patients	301 (100)	205 (68)	95 (32)	–
Year				1
2004–2008	175 (58)	119 (68)	55 (32)	
2009–2013	126 (42)	86 (68)	40 (32)	
Induction regimen				1
AcDVP16	284 (94)	193 (68)	90 (32)	
AcIVP16	17 (6)	12 (71)	5 (29)	
Gender				1
Male	161 (53)	109 (68)	51 (32)	
Female	140 (47)	96 (69)	44 (31)	
Age				0.02 ^b
<60	222 (74)	160 (72)	61 (28)	
60	79 (26)	45 (57)	34 (43)	
70	5 (2)	1 (20)	4 (80)	
Age – median	52 (20–74)	52 (20–74)	52 (20–73)	0.09
Cytogenetics				< 0.0001
Favorable	24 (8)	22 (96)	1 (4)	
Intermediate	180 (60)	133 (74)	47 (26)	
Unfavorable	94 (31)	49 (52)	45 (48)	
Missing	3 (1)	1 (33)	2 (67)	
Leukemia type				0.0003
De Novo	205 (68)	154 (75)	51 (25)	
Secondary	96 (32)	51 (54)	44 (46)	
Peripheral WBC				0.9
<50 × 10 ⁹ /L	230 (76)	157 (69)	72 (31)	
50 × 10 ⁹ /L	71 (24)	48 (68)	23 (32)	
WBC (×10 ⁹ /L)	15 (0.1–396)	15 (0.1–396)	13 (0.5–235)	0.3
FLT3-ITD status				1
Positive	55 (18)	40 (73)	15 (27)	
Negative	206 (68)	148 (72)	58 (28)	
Missing	40 (13)	17 (44)	22 (56)	

Abbreviations: AcDVP16, cytarabine + daunorubicin + etoposide timed sequential therapy; AcIVP16, cytarabine + idarubicin + etoposide timed sequential therapy; AML, acute myelogenous leukemia; CR, complete remission; No., number; WBC, white blood cell count; FLT3-ITD, Fms-like tyrosine kinase 3 internal tandem duplication.

^aOne patient had missing CR information.

^bp-value for comparison of <60 and ≥60 years of age.

Table 2

Univariate analysis for overall survival and disease-free survival with p-values reflecting the Cox proportional hazards model.

Variables	No. (%)	Median (mos)	OS % 5-year (95% CI)	HR (95% CI)	p-value	No (%)	DFS Median (mos)	% 5-year (95% CI)	HR (95% CI)	p-value
All patients	301 (100)	17.2	32 (27–38)	–	–	205 (100)	15.0	37 (31–45)	–	–
Year										
2004–2008	175 (58)	18.2	31 (25–39)	1	–	119 (58)	15.0	35 (27–45)	1	–
2009–2013	126 (42)	17.2	35 (26–46)	0.9 (0.7–1.2)	0.6	86 (42)	18.0	39 (28–54)	0.9 (0.6–1.3)	0.6
Age										
<60	222 (74)	26.1	38 (32–46)	1	–	160 (78)	22.4	42 (35–51)	1	–
60	79 (26)	10.7	14 (8–26)	2.1 (1.5–2.8)	<0.0001	45 (22)	10.9	19 (10–36)	1.9 (1.3–2.8)	0.002
Cytogenetics										
Favorable	24 (8)	55.7	46 (28–76)	1	–	22 (11)	13.3	39 (22–68)	1	–
Intermediate	180 (60)	24.8	38 (31–46)	1.3 (0.7–2.4)	0.4	133 (65)	22.3	39 (32–49)	0.9 (0.5–1.6)	0.7
Unfavorable	94 (31)	8.2	19 (12–30)	2.6 (1.4–5.0)	0.003	49 (24)	9.2	30 (20–47)	1.5 (0.8–2.9)	0.2
Leukemia type										
De Novo	205 (68)	19.0	35 (29–43)	1	–	154 (75)	17.4	39 (32–48)	1	–
Secondary	96 (32)	13.9	26 (18–37)	1.4 (1.0–1.9)	0.03	51 (25)	14.4	31 (20–48)	1.2 (0.8–1.7)	0.4
Peripheral WBC										
<50 × 10 ⁹ /L	230 (76)	18.9	34 (28–41)	1	–	157 (76)	17.4	38 (31–47)	1	–
50 × 10 ⁹ /L	71 (24)	16	26 (17–40)	1.2 (0.8–1.6)	0.3	48 (23)	13.2	34 (23–52)	1.1 (0.7–1.6)	0.8
FLT3-ITD status										
Negative	206 (68)	17.1	31 (25–38)	1	–	148 (72)	14.8	36 (29–45)	1	–
Positive	55 (18)	18.4	37 (26–53)	0.9 (0.6–1.3)	0.5	40 (19)	15.6	41 (28–60)	0.9 (0.6–1.4)	0.6

Abbreviations: AcDVP16, cytarabine + daunorubicin + etoposide timed sequential therapy; AcVP16, cytarabine + idarubicin + etoposide timed sequential therapy; AML, acute myeloid leukemia; CI, confidence interval; DFS, disease-free survival; mos, months; FLT3-ITD, Fms-like tyrosine kinase 3 internal tandem duplication; HR, hazard ratio; No., number; OS, overall survival; WBC, white blood cell count.

Table 3

Summary of results with TST induction compared to 7 + 3 reported in the literature.

Study/arm	No.	Median Age (y)	Cytogenetics (%)			Follow-up (y) ^a	CR rate (%)	Early ^b death (%)	Median days to ANC 500/ μ L (range) ^c	Median or % (95% CI)		
			Low	Intermediate	High					OS (mos) ^d	5-year OS (%)	DFS (mos)
TST												
Current	301	52	8	60	31	5.8	68	8	34 (17–115)	17.2 (15–24.6)	32 (27–38)	15 (13.2–29.5)
ALFA-9000 ³²	197	45	9	34	15	9.8	74	16	30	NA	32 (26–40)	NA ^e
DCTER ³⁵	61	41	0	70	25	5.6	71	3 ^f	36 (27–98)	24 ^g	41 ^g	16 ^g
7+3 ^h												
ALFA-9000 ³²	197	46	10	41	12	9.8	77	12	25	NA	28 (22–35)	NA ^e
ALFA-0701 ³³ /7+3 arm	139	62	4	65	22	1.7	72	4	22 (18–27)	19.2 (13.8–26)	NA	11.4 (9.9–14.5)
AML17 ³¹ /60mg/m ²	602	53	10	68	16	1.2	75	5	30	Not reached	NA	NA
AML17 ³¹ /90mg/m ²	604	53	7	69	18	1.2	73	10	30	Not reached	NA	NA
ECOG ³⁴ /45mg/m ²	330	47	12	43	18	2.1	57	5	NA	15.7	20 ^g	NA
ECOG ³⁴ /90mg/m ²	327	48	16	39	19	2.1	71	6	NA	23.7	35 ^g	NA

Abbreviations:: ANC, absolute neutrophil count; CI, confidence interval; CR, complete remission; DFS, disease-free survival; mos, months; NA, not available; OS, overall survival; y, years.

^aReversed Kaplan-Meier method (current publication), not defined (ALFA-9000), median follow-up in survivors (DCTER, FLAM, ALFA-0701, AML17, and ECOG).

^bDefined as death within 60 days (not defined in ALFA-0701). ALFA-9000 defined as deaths between start of induction and evaluation of response to induction or induction/salvage therapy.

^cRange not always reported. DCTER reported median time to CR.

^d95% CI not always reported.

^eALFA-9000 5-year EFS 25% (95% CI 19–33) for TST, 16% (95% CI 11–23) for 7 + 3.

^f3 additional patients died days 66, 71, and 74 of chemotherapy without achieving count recovery. Inclusion of these patients would make induction deaths 8%.

^gEstimated from Kaplan-Meier curves in paper.

^hAML17 trial used cytarabine 100 mg/m² every 12 h days 1–10 with daunorubicin 60 or 90 mg/m² days 1, 3, and 5.