

A Comparison of High-Dose Cytarabine During Induction Versus Consolidation Therapy in Newly Diagnosed AML

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Abstract

The proportion of patients with acute myeloid leukemia (AML) cured is increased by administering high-dose cytarabine (HiDAC). It remains uncertain whether to administer HiDAC as induction or consolidation, and whether ≥ 1 cycle of HiDAC is required. Our retrospective study of 416 adult AML patients, excluding good risk cytogenetics, compared a single cycle of HiDAC-based therapy followed by 2 cycles of standard-dose cytarabine (SDAC) (HiDAC induction cohort) with SDAC-based chemotherapy followed by 2 cycles of HiDAC-based chemotherapy (HiDAC consolidation cohort). Complete remission (CR) rate was greater in the HiDAC induction cohort (90% vs 78%, $P < 0.01$) which did not lead to an improved overall survival (48% vs 43%, $P = 0.18$) or disease-free survival (DFS) (39% vs 45%, $P = 0.95$). We noted that, after censoring for allogeneic hematopoietic stem cell transplant (alloHSCT) in CR1, the cumulative incidence of relapse was lower in the HiDAC consolidation cohort in patients with intermediate risk cytogenetics (68% vs 44%, $P = 0.01$), which lead to a greater DFS (30% vs 47%, $P = 0.095$). In the patients with adverse risk cytogenetics, the RR was numerically greater in the HiDAC consolidation cohort (52% vs 80%, $P = 0.60$) which lead to a lower DFS (27% vs 4%, $P = 0.11$). Our data show that, although the HiDAC induction cohort (1 cycle of HiDAC) achieved a greater CR rate, there were no overall survival differences between the 2 cohorts, and that the HiDAC consolidation cohort (2 cycles of HiDAC) had a lower RR and greater DFS in those patients with intermediate risk cytogenetics who did not undergo alloHSCT in CR1.

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INTRODUCTION

Multiple cycles of chemotherapy cure a proportion of younger patients with acute myeloid leukemia (AML) with the combination of an anthracycline and cytarabine remaining the standard of care for younger, medically fit patients.¹⁻³ The introduction of high-dose cytarabine-based (1-3 g/m²) chemotherapy (HiDAC), given for one or more cycles, has increased the proportion of patients with AML cured of their disease compared with standard-dose cytarabine-based (100-200 mg/m²) chemotherapy (SDAC).^{4,5} Accordingly, there is general agreement that HiDAC should be included in the therapy of younger AML patients (aged <60-65 years), although it remains uncertain whether it is best given as induction therapy, consolidation therapy or both, for how many cycles and at what dose.^{6,7} Most cooperative groups such as HOVON/SAKK,⁸ MRC,⁹ GOELAMS,¹⁰ German AMLCG,^{11,12} UK NCRI,¹³ and CALGB¹⁴ have used SDAC as induction and HiDAC as consolidation. HiDAC as induction therapy has been explored by several groups including the EORTC-GIMEMA,¹⁵ the ALLG (formerly ALSG),⁵ SWOG,¹⁶ and the German AMLCG¹⁷—based on the hypothesis that HiDAC as induction therapy will induce a better initial tumor cell kill and circumvent the development of resistance. Some groups have studied HiDAC as both induction and consolidation—ALLG,¹⁸ HONVON/SAKK,¹⁹ SWOG,¹⁶ German AMLCG.^{20,21} The current NCCN Guidelines indicate that HiDAC either as induction therapy or consolidation therapy is acceptable.²² The

current ELN Guidelines³ recommend 7 days of standard dose cytarabine and 3 days of an anthracycline (7+3) as induction therapy followed by 2 to 4 cycles of HiDAC (1–1.5 g/m² BD) without anthracycline as consolidation. No randomized study has addressed the question of whether HiDAC is best given as induction or consolidation therapy, nor the issue of the optimal number of cycles of HiDAC; some studies have used multiple cycles of HiDAC usually during consolidation^{4,9,13,14} or during induction and consolidation,^{12–14,16,17,20,21} whereas others have used a single cycle of HiDAC as induction^{5,17} or consolidation.^{8,10,11,16} Comparisons between studies are confounded by different patient populations, cytarabine and anthracycline doses as well as the rates of allogeneic hematopoietic stem cell transplantation (alloHSCT) in first complete remission (CR1), and incidences of treatment-related mortality (TRM)—these latter 2 confounders make it difficult to assess the antileukemic efficacy of the chemotherapy per se.

We performed a retrospective analysis of induction versus consolidation use of HiDAC in a cohort of patients, aged from 18 to ≤60 years, from 5 Australian hospitals, who presented with a new diagnosis of AML, excluding those with good risk cytogenetics, over a 14-year period, and were planned to receive either HiDAC-based induction therapy followed by 2 cycles of a short course of SDAC-based consolidation therapy (HiDAC induction cohort), or SDAC-based induction therapy followed by 2 cycles of HiDAC-based consolidation therapy (HiDAC consolidation cohort)—the 2 commonest approaches to AML treatment in Australia. We compared the outcomes of these 2 cohorts.

PATIENTS AND METHODS

Study cohorts

Eligibility consisted of the following: age 18 to ≤60 years; new diagnosis of de novo or secondary AML (excluding patients with good risk cytogenetics) treated at one of five Australian Hospitals from 1999 to 2013; and planned for treatment with either HiDAC-based induction therapy followed by 2 cycles of short course SDAC-based consolidation therapy, or SDAC-based induction therapy followed by 2 cycles of HiDAC-based consolidation therapy. Data cut-off was June 30, 2014 enabling a minimum of a 12 months follow-up for all patients. The study was approved by the Eastern Health Human Research Ethics Committee.

Chemotherapy regimens

The choice of which chemotherapy each patient received varied at each institution and over the years based on then current institutional protocols or clinical trials.

HiDAC induction cohort (n=205)

Induction therapy consisted of one of 2 regimens: HiDAC-37 (n=173) consisting of cytarabine 3 g/m² BD on days 1, 3, 5, and 7, idarubicin 9 to 12 mg/m² on days 1 to 3, and etoposide 75 to 100 mg/m² on days 1 to 7; or, HiDAC-3 (n=32) consisted of cytarabine 3 g/m² BD on days 1, 3, 5, and 7 and idarubicin 12 mg/m² on days 1 to 3. If CR was not achieved, the patient usually received a second cycle of the same induction therapy. If CR was not achieved after the second induction cycle, the patient was deemed to have primary refractory disease. Planned consolida-

tion therapy after CR for this cohort consisted of 2 cycles of cytarabine 100 mg/m² as a continuous infusion for 5 days plus idarubicin 9 to 12 mg/m² on days 1 and 2 ± etoposide 75 to 100 mg/m² for 5 days (52 ± 5).

HiDAC consolidation cohort (n=211)

Induction therapy for all patients consisted of 7+3—cytarabine 100 mg/m² as a continuous infusion for 7 days with idarubicin 12 mg/m² on days 1 to 3. Consolidation therapy after CR for this cohort was 2 cycles of HiDAC 3 g/m² BD 1, 3, 5, and 7 plus idarubicin 9 to 12 mg/m² on days 1 and 2 (HiDAC-2). If CR was not achieved after the initial induction cycle, the patient usually received a cycle of HiDAC-3, which consisted of HiDAC 3 g/m² BD 1, 3, 5, and 7 plus idarubicin 9 to 12 mg/m² on days 1 to 3. If CR was then obtained the patient received one additional cycle of HiDAC-2 as consolidation.

Risk stratification

Cytogenetic abnormalities were classified as intermediate risk or adverse risk according to the MRC classification.²³ Mutational molecular data, such as FLT3-ITD and NPM1, were not available for the majority of patients.

Statistics

To address the bias introduced by the nonrandom allocation to cohort, propensity scores (modeling the probability of being in the HiDAC induction cohort) were derived²⁴ using logistic regression. The covariates used in the model included gender, AML etiology (primary, secondary, unknown), cytogenetic risk stratification (intermediate, adverse, unknown), year of diagnosis, age group (≤40, >40) and WCC at diagnosis category (<50, ≥50 to <100, ≥100). The propensity scores were divided into quintiles which were then used as a stratifying variable in all analyses.

Response rates were compared between cohorts using a stratified Cochran Mantel Haenszel test. The relative risk of response (HiDAC induction cohort/HiDAC consolidation cohort) corrected for propensity score quintile was estimated with 95% confidence limits. The analysis was conducted for all patients and separately according to cytogenetic risk stratification: intermediate and adverse. TRM and receipt of alloHSCT were analyzed in similar way.

Overall survival (OS) was defined as the time from diagnosis until death from any cause. Disease-free survival (DFS) was defined as the time from the attainment of CR until relapse or death from any cause. OS and DFS were analyzed using a Cox proportional hazards model with cohort, cytogenetic risk level and propensity score quintile as factors in the model. From this model the hazard ratio (HR) for HiDAC induction cohort/HiDAC consolidation cohort was estimated with 95% confidence limits. The estimated HR overall and by cytogenetic risk level (intermediate or adverse) was obtained from the same model (together with *P* values). Time to relapse was analyzed using a Cox proportional hazards model with death as a competing risk using the methods described by Fine and Gray.²⁵ The model was fitted with cohort, cytogenetic risk level and propensity score quintile as factors in the model.

Sensitivity analyses were performed to explore the impact of transplant by censoring at the time of transplant.

Five-year survival rates were estimated from unstratified Kaplan–Meier analyses using the life table method.

For pragmatic reasons, CR was defined as a bone marrow aspirate with morphologically <5% blasts independent of neutrophil and platelet counts in the peripheral blood, hence, including CRi and CRp.

RESULTS

Demographics

Over the 14-year period, 416 eligible patients were identified (Table 1). There were 205 patients in the HiDAC induction cohort planned for HiDAC-3 ± 7 induction followed by 2 cycles of 52 ± 5 consolidation, and 211 patients in the HiDAC consolidation cohort planned for 7 + 3 induction followed by 2 cycles of HiDAC-2 consolidation. The median follow-up of surviving patients in each cohort was 5.5 and 5.6 years, respectively. The 2 cohorts were reasonably matched for demographics and baseline characteristics except that more patients in the HiDAC induction cohort had missing data regarding whether the AML was de novo or secondary (36% vs 4%, $P < 0.01$). To adjust the data for potential bias in the nonrandom allocation of patients to each treatment group, the propensity score method was used.

A contour diagram (Fig. 1) shows the distribution and outcomes of the patients in both the HiDAC induction and HiDAC consolidation cohorts.

Response rates

The CR rate after the initial induction therapy (HiDAC-3 ± 7 vs 7 + 3) was greater in the HiDAC induction cohort than that of the HiDAC consolidation cohort (85% vs 67%, $P < 0.01$) (Table 2). The CR rate improved in both cohorts after the completion of all therapy (reinduction, if required, and all consolidation therapies) but remained significantly greater in the HiDAC induction cohort compared with the HiDAC consolidation cohort (90% vs 78%, $P < 0.01$). TRM during the initial induction chemotherapy was

low in each group (HiDAC induction cohort 5% and HiDAC consolidation cohort 5%, $P = 0.90$). The TRM at the end of all induction and consolidation cycles remained at 5% for the HiDAC induction cohort but increased to 8% in the HiDAC consolidation cohort ($P = 0.28$).

For patients with intermediate risk cytogenetics, CR rate was numerically greater in the HiDAC induction cohort compared to the HiDAC consolidation cohort: post the initial induction chemotherapy: 89% versus 81%, $P = 0.17$; and after all therapy: 94% versus 87%, $P = 0.07$. For patients with adverse risk cytogenetics the CR rate was significantly greater in the HiDAC induction cohort: after initial induction chemotherapy: 69% versus 33%, $P < 0.01$; and after all therapy: 71% versus 56%, $P = 0.03$.

Overall survival

There was no statistical difference in the estimated 5-year OS between the HiDAC induction and HiDAC consolidation cohorts (48% vs 43%; HR 1.26, CL 0.90–1.77, $P = 0.18$), despite the statistically greater CR rate in the HiDAC induction cohort (Figs. 2–4). The majority of the patients fell into the intermediate risk cytogenetic subset (73%) and the results in this subset reflected that of the entire cohort with no significant difference in OS (52% vs 54%; HR 1.04, CL 0.73–1.48, $P = 0.81$). The greater CR rate in the adverse risk cytogenetic subset led to a numerically but not statistically greater OS in the HiDAC induction cohort (29% vs 18%; HR 1.52 CL 0.88–2.62, $P = 0.13$).

Disease-Free Survival

DFS was not statistically different between the HiDAC induction and HiDAC consolidation cohorts (5-year DFS 39% vs 45%; HR 0.99, CL 0.66–1.47, $P = 0.95$) (Figs. 2–4). This was similar for the group of patients with intermediate risk cytogenetics (5-year DFS 38% vs 46%; HR 0.86, CL 0.61–1.22, $P = 0.40$), and the group of patients with adverse risk cytogenetics (5-year DFS 31% vs 29%; HR 1.13 CL 0.57–2.25, $P = 0.73$).

Table 1

Patient Demographics

	HiDAC Induction, n=205	HiDAC Consolidation, n=211	P	Adjusted P (Propensity Score)
Median age (y) (range)	47.2 (18–60.6)	49.9 (18–60.9)	0.70	0.95
Sex			0.55	0.94
Male	108 (53%)	105 (50%)		
Female	97 (47%)	106 (50%)		
Year of diagnosis			0.04	1.0
2000–2006	88 (43%)	110 (52%)		
2007–2013	117 (57%)	101 (48%)		
AML			<0.01	0.80
Primary	107 (52%)	165 (78%)		
Secondary	24 (12%)	37 (18%)		
Unknown	74 (36%)	9 (4%)		
White cell count at diagnosis n × 10 ⁹ /L (range)	9.3 (0.6–356.0)	7.4 (0.4–265.0)	0.32	0.99
Cytogenetic risk group			<0.01	0.55
Intermediate	166 (81%)	136 (64%)		
Adverse	35 (17%)	52 (25%)		
Unknown	4 (2%)	23 (11%)		

AML = acute myeloid leukemia, HiDAC = high-dose cytarabine.

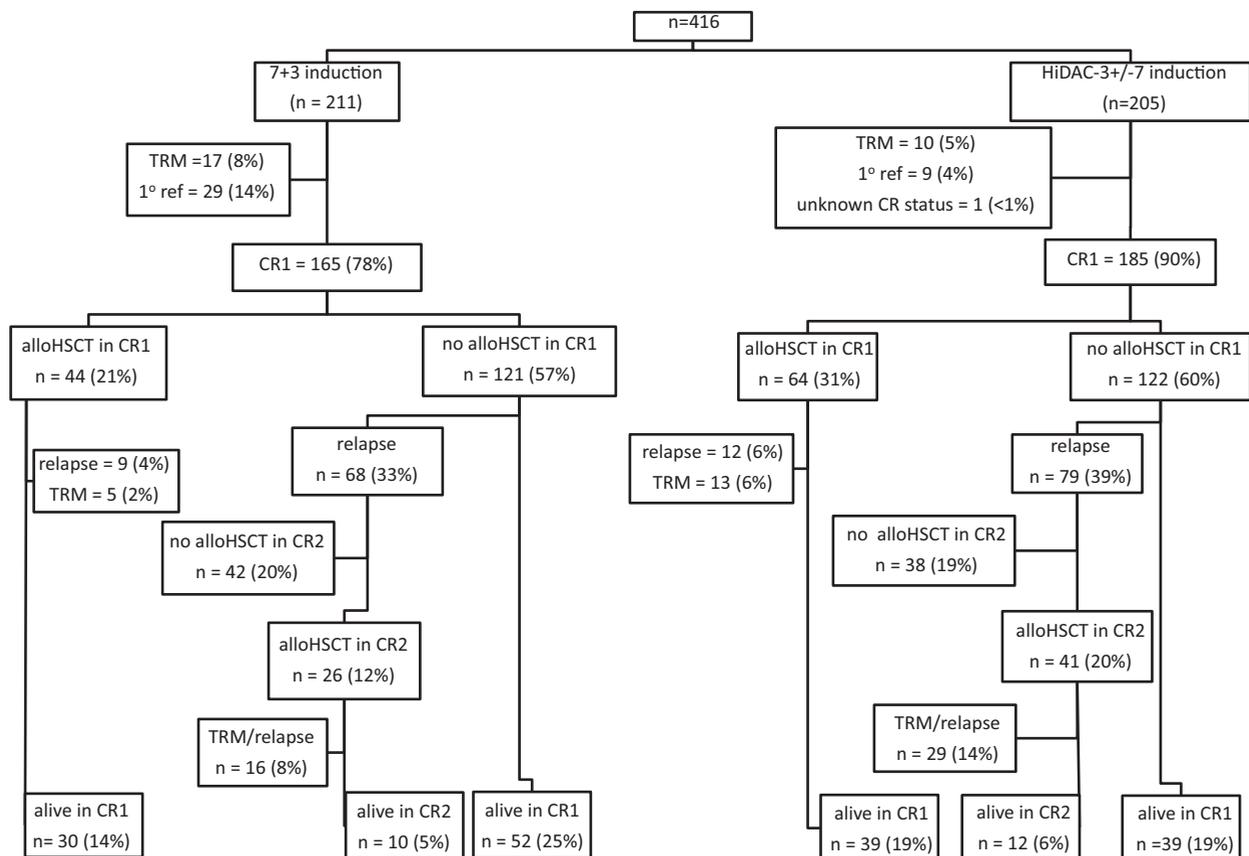


Figure 1. Consort diagram. The consort diagram shows the distribution and outcomes of patients in the both the HiDAC induction and HiDAC consolidation cohorts. The addition of the percentages is slightly out due to rounding errors. 1° ref=primary refractory, alloHSC=allogeneic hematopoietic stem cell transplantation, CR1=first complete remission, CR2=second complete remission, TRM=treatment related mortality.

AlloHSC

There were no uniform criteria for which patients should be considered for alloHSC. The decision whether a patient moved to alloHSC varied at each institution and varied over the years. AlloHSC was performed more frequently in the HiDAC induction cohort compared to the HiDAC consolidation cohort—105 versus 76 patients (51% vs 36%, $P < 0.01$) most commonly performed in CR1 (31% vs 21%, $P = 0.055$). This was

predominantly due to an increased alloHSC rate in the subgroup with intermediated risk cytogenetics—86 (52%) versus 50 (37%) $P = 0.019$. Of those who achieved CR1, 64 of 185 (35%) patients in the HiDAC induction cohort and 44 of 164 patients (27%) in the HiDAC consolidation cohort underwent the alloHSC in CR1 ($P = 0.16$). Again, this difference appeared to be greater in the subgroup with intermediate risk cytogenetics—51 of 156 (33%) versus 26 of 118 (22%) $P = 0.096$. The 5-year

Table 2

Outcomes

	HiDAC Induction		HiDAC Consolidation		RR	95% CL	P
CR post 1st induction therapy							
All patients	175/205	85%	141/211	67%	0.84	0.74, 0.94	<0.01
Intermediate risk cytogenetics	148/166	89%	110/136	81%	0.93	0.83, 1.04	0.17
Adverse risk cytogenetics	24/35	69%	17/52	33%	0.42	0.25, 0.72	<0.01
Cytogenetics not known	3/4	75%	14/23	61%	—	—	—
TRM post 1st induction therapy	10/205	5%	11/211	5%	1.08	0.33, 3.50	0.90
Final CR							
All patients	185/205	90%	164/211	78%	0.87	0.80, 0.96	<0.01
Intermediate risk cytogenetics	156/166	94%	118/136	87%	0.92	0.84, 1.01	0.07
Adverse risk cytogenetics	25/35	71%	29/52	56%	0.67	0.47, 0.95	0.03
Cytogenetics not known	4/4	100%	17/23	74%	—	—	—
Final TRM	10/205	5%	17/211	8%	1.77	0.61, 5.09	0.28

CR=complete remission, HiDAC=high-dose cytarabine, RR=relapse rates, TRM=treatment-related mortality.

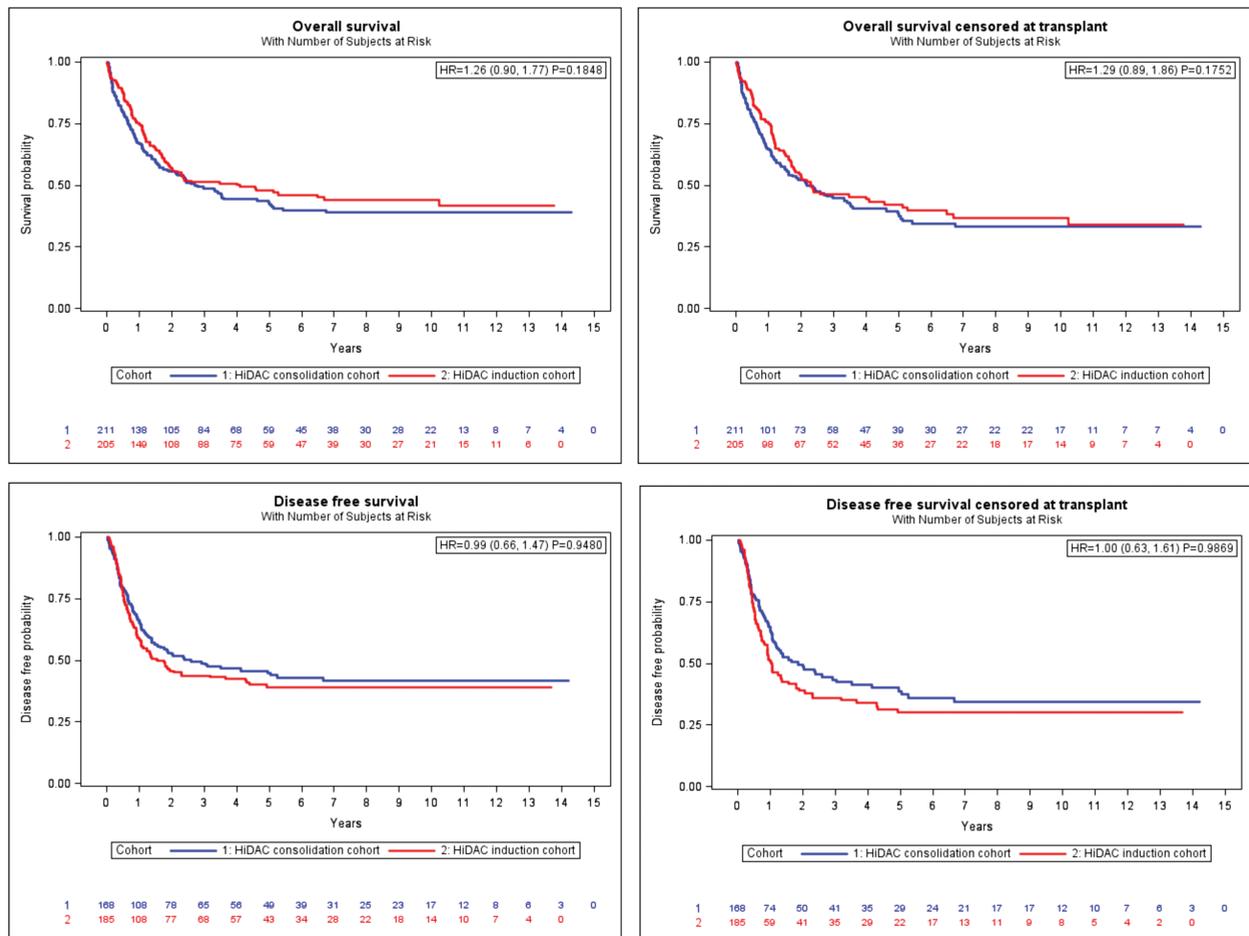


Figure 2. Outcomes of entire cohort. Entire cohort: OS and DFS. Censored for alloHSCT in CR1: OS and DFS.

OS of patients undergoing alloHSCT in CR1 was similar in both the HiDAC induction cohort and the HiDAC consolidation cohort (5-year OS; 61% vs 61%, $P=ns$).

Relapse

There was no statistically significant difference in the relapse rates (RR) with death as a competing factor between the HiDAC induction and the HiDAC consolidation cohorts (5-year RR 51% vs 44%; HR 1.08, CL 0.67–1.74, $P=0.76$). In the subgroup with adverse risk cytogenetics the RR was numerically greater in the HiDAC consolidation cohort (5-year RR 48% vs 60%; HR 1.53, CL 0.67–3.46, $P=0.31$) although in the subgroup with intermediate risk cytogenetics the RR was numerically greater in the HiDAC induction cohort (5-year RR 52% vs 38%, HR 0.76, CL 0.51–1.14, $P=0.19$).

Censoring for alloHSCT in CR1

The outcomes of patients undergoing alloHSCT in CR1 were similar in both the HiDAC induction and HiDAC consolidation cohorts, and better than the outcomes of the cohorts as a whole (Figs. 2–4). Therefore, to assess the efficacy of the chemotherapy alone, the cohorts were analyzed with censoring for alloHSCT in CR1.

After censoring for alloHSCT in CR1, OS did not differ significantly between the 2 cohorts (5-year OS 42% vs 39%, HR 1.29, CL 0.89–1.86, $P=0.17$), nor did the RR (5-year RR 69% vs 52%, HR 0.88, CL 0.51–1.52, $P=0.65$), nor did the DFS (5-year DFS 30% vs 39%, HR 1.00 CL 0.63–0.99, $P=0.99$).

After censoring for alloHSCT in CR1, the outcomes did appear to differ depending on the cytogenetic subgroup—the subgroup with intermediate risk cytogenetics appeared to benefit from HiDAC consolidation with respect to RR (5-year RR 68% vs 44%, HR 0.60, CL 0.40–0.9, $P=0.014$) and DFS (5-year DFS 30% vs 47%, HR 0.73, CL 0.50–1.06, $P=0.095$) although there were no statistical differences in OS (5-year OS 46% vs 51%; HR 0.96, CL 0.66–1.41, $P=0.85$). For the subgroup with adverse risk cytogenetics, there was a trend for greater OS (5-year OS 28% vs 5%; HR 1.73, CL 0.95–3.15, $P=0.08$) in the HiDAC induction cohort but with no statistical differences in DFS (5-year DFS 38% vs 8%; HR 1.39, CL 0.60–3.22, $P=0.44$) or RR (5-year RR 52% vs 80%; HR 1.30, CL 0.48–3.51, $P=0.60$).

DISCUSSION

AML is an aggressive disease that was uniformly fatal until the advent of intensive cytarabine and anthracycline-based chemotherapy. SDAC-based therapy cures 10% to 30% of younger

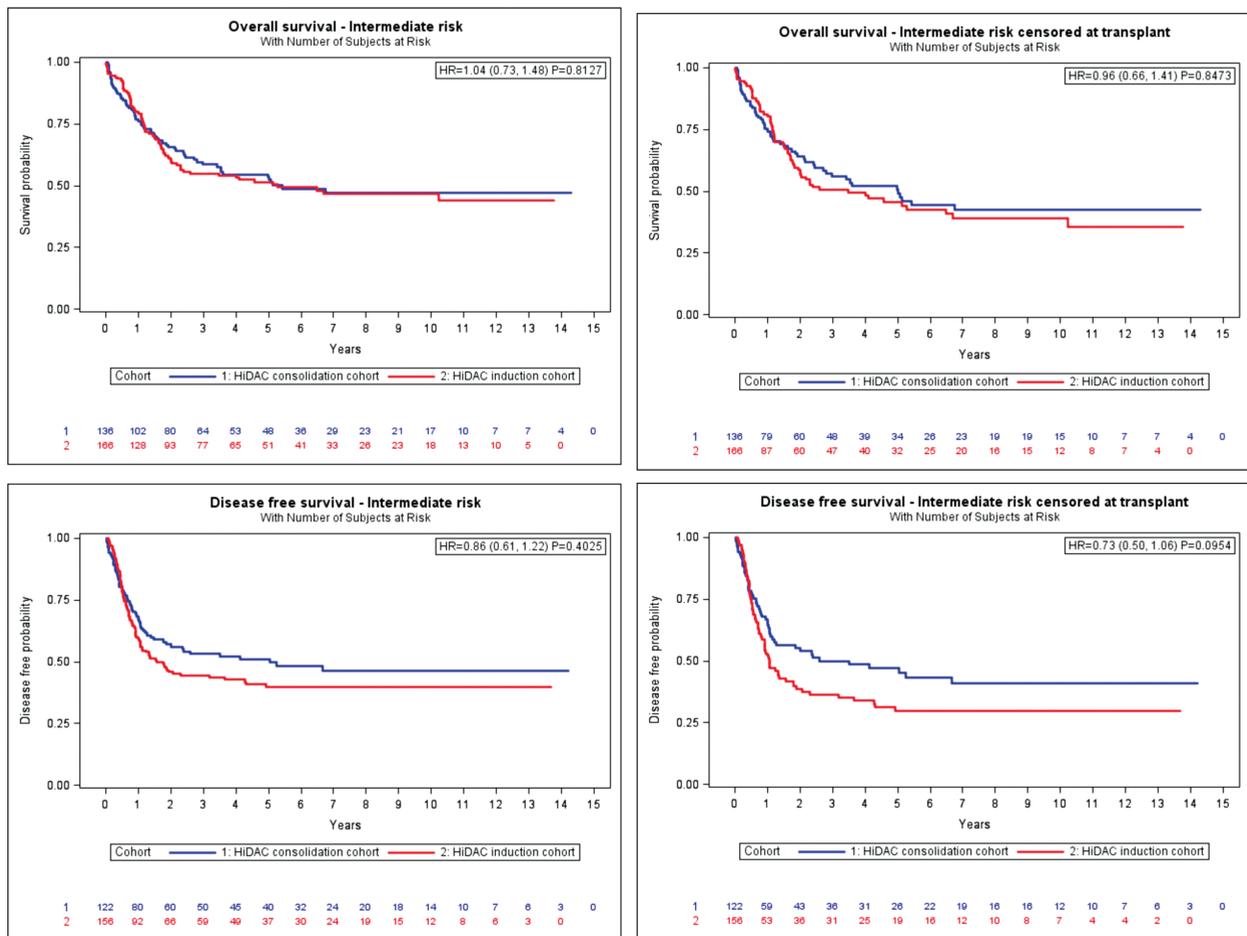


Figure 3. Outcomes of patients with intermediate risk cytogenetics. Entire cohort: OS and DFS. Censored for alloHSCT in CR1: OS and DFS.

patients.^{4,5,16,17} The seminal CALGB⁴ study showed that HiDAC used as consolidation, once complete remission (CR) had been achieved, increased the proportion of patients cured from 31% versus 46%. Since then, several cooperative groups have explored the use of HiDAC (1–3 g/m²) as induction therapy^{5,15,18,19} or as consolidation therapy^{16,17,19} or as both induction and consolidation therapy.^{16,18,19} Thus, most cooperative groups and physicians consider HiDAC-based therapy as an integral part of the treatment of younger patients with newly diagnosed AML, although it remains uncertain whether HiDAC-based therapy is best given as induction, or as consolidation, or both as induction and consolidation, or for how many cycles.^{3,22}

Our study is a retrospective analysis of real-world experience with HiDAC-based treatment as induction or consolidation therapy with long-term follow-up of 416 consecutive patients. We noted an 18% greater CR rate (85% vs 67%, $P < 0.01$) after the first cycle of chemotherapy in the HiDAC induction cohort (HiDAC-3 ± 7) compared to the HiDAC consolidation cohort (7 + 3) which remained significantly greater (90% vs 78%, $P < 0.01$) after the completion of all cycles of induction and consolidation chemotherapy. The improved CR rate with HiDAC-based induction therapy compared to SDAC-based induction therapy was also noted in the EORTC-GIMEMA study,¹⁵ although other, mostly older, studies have shown no differences.^{5,16,17,19} The ALLG M4 study⁵ showed that more patients required 2

induction therapies with SDAC to achieve the same CR rate as HiDAC although this was not confirmed in a more recent study by HOVON/SAKK.¹⁹ The relatively low induction TRM in our study minimized the confounding effect of TRM on CR rates. The ALLG M4 study⁵ showed a higher death rate during induction in the HiDAC induction arm compared to the SDAC induction arm (18% vs 11%, $P = 0.09$) as did the SWOG study¹⁶—14% versus 5% for those aged <50 years and 20% versus 12% for those aged 50 to 64 years, $P < 0.01$. However, the more recent HOVON/SAKK study¹⁹ showed the same low early death rate (4% vs 4%) in the HiDAC and SDAC induction arms and still did not find a difference in the CR rate between the 2 arms.

The key observation from our study is that despite the greater CR rate (90% vs 78%) with HiDAC induction and the higher rate of alloHSCT in CR1 (31% vs 21%), there was no improvement in the OS, DFS, or RR (Figs. 2–4) compared to the HiDAC consolidation cohort. These findings are somewhat counterintuitive but there are several possible explanations. Perhaps once CR is obtained, 2 cycles of HiDAC as consolidation (HiDAC consolidation cohort) are more effective at curing the patient compared with 2 cycles of SDAC (HiDAC induction cohort); or perhaps that HiDAC-based induction therapy, as a more intensive regimen, is better able to achieve a morphological CR but the increased proportion includes mostly patients with intrinsically resistant disease

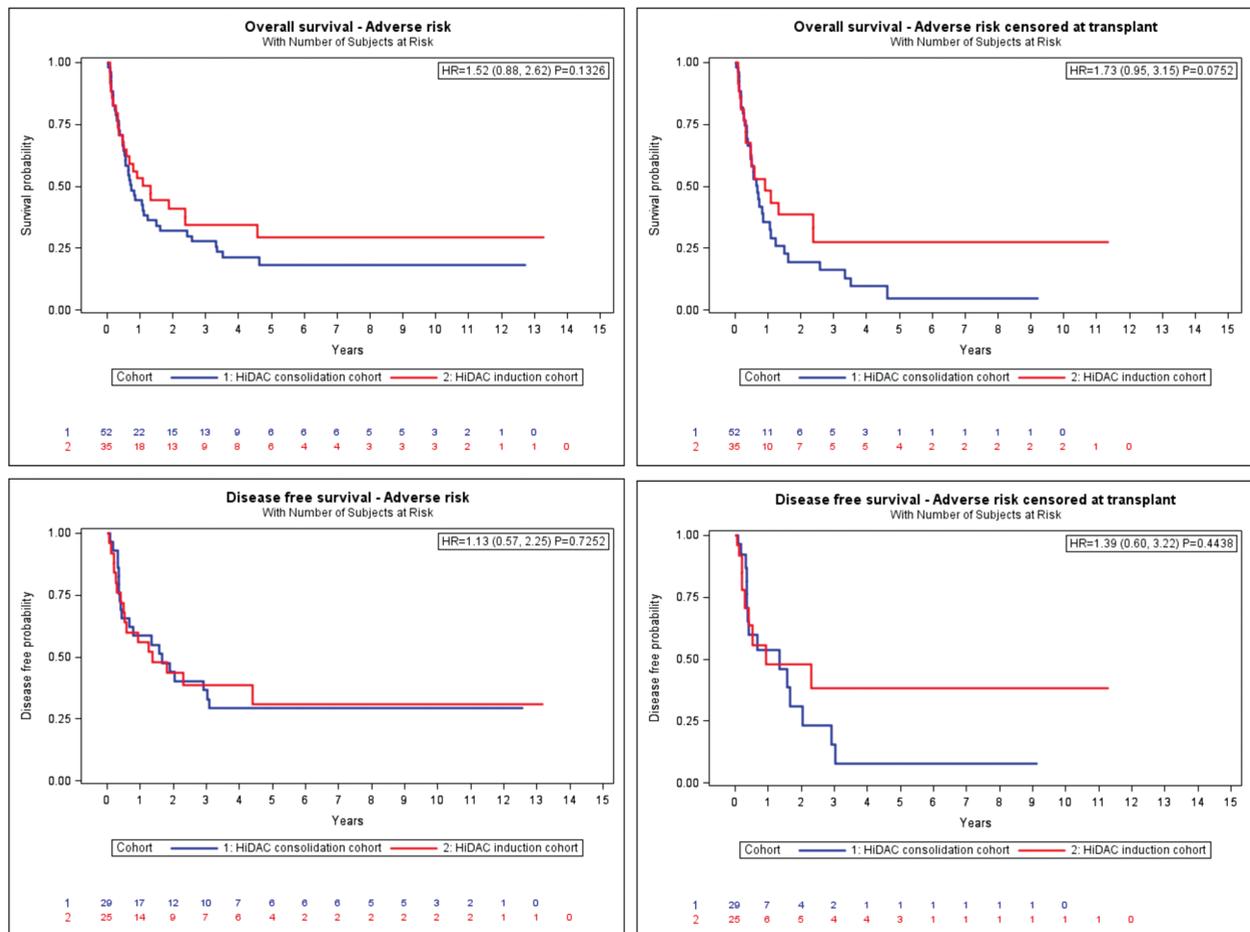


Figure 4. Outcomes of patients with adverse risk cytogenetics. Entire cohort: OS and DFS. Censored for alloHSCt in CR1: OS and DFS.

which is destined to relapse; or perhaps there were other unmeasured or unknown risk factors that were imbalanced between the 2 cohorts, such as the molecular mutations of FLT3, NPM1, and others.

The efficacy of chemotherapy regimens at curing patients with AML is confounded by TRM and alloHSCt in CR1—the greater the TRM and the greater the alloHSCt rate in CR1, the more difficult it becomes to assess how effective any particular chemotherapy regimen is at curing patients with AML. In our study, the TRM in both cohorts was low (5% vs 8%, $P=0.28$), but there was a significant difference in the alloHSCt in CR1 rate favoring the HiDAC induction cohort (31% vs 21%, $P=0.055$). Hence, to better assess the efficacy of the chemotherapy itself, the cohorts were also analyzed after censoring for alloHSCt in CR1—the outcomes appeared to differ depending on the cytogenetic subgroup. Those patients with adverse cytogenetics, although the numbers were relatively small, appeared to do better in the HiDAC induction cohort with the greater CR rate (71% vs 56%, $P=0.03$) translating into a trend for a greater OS and DFS with a numerically lower RR. On the other hand, in the subgroup of patients with intermediate risk cytogenetics, the greater CR rate in the HiDAC induction cohort (94% vs 87%, $P=0.07$) did not translate into a better outcome with no difference in OS between the 2 cohorts, perhaps due to the greater RR in those patients who achieved CR1 after receiving a single cycle of HiDAC (HiDAC induction cohort) but did not under alloHSCt in CR1 compared

to the matching group of patients undergoing 2 cycles of HiDAC (HiDAC consolidation cohort)—which translated into a greater DFS in this subgroup.

To date, no randomized study has compared HiDAC as induction therapy with HiDAC as consolidation therapy. There is no clear difference in outcomes when the various studies are compared with each other.⁶ The SWOG¹⁶ study seemed to show an improved outcome for HiDAC given as induction and consolidation although the ALLG study¹⁸ did not show such an advantage.

Most studies have used multiple cycles of HiDAC and many studies use the cytarabine alone without additional anthracyclines. Some authors²⁶ suggest that a single course of HiDAC without anthracycline is sufficient to maximize the cure rate of patients with newly diagnosed AML, and suggest that the dose of cytarabine should be limited to 1 to 1.5 g/m² for reasons of toxicity. Supporting this last point is a recent meta-analysis of the randomized studies of patients undergoing induction/consolidation therapy for newly diagnosed AML who did not proceed to alloHSCt which did not find any OS differences, in any cytogenetic risk group, between the high-dose cytarabine (total dose >20 g) and the intermediate-dose and low-dose cytarabine (total dose <20 g).²⁷

Our data do not address the questions of the dose of HiDAC or whether or not the addition of an anthracycline in consolidation is necessary to maximize the cure rate of patients with newly

diagnosed AML. Our data do suggest that HiDAC-based therapy as induction gives a greater CR rate, and our data also suggest that a single course of HiDAC-based therapy may not be adequate to maximize the rate of cure in those patients who are not planned to undergo alloHSCT in CR1. In the most recent ALLG study (M12),²⁸ all patients received a single cycle of HiDAC-3 as induction therapy, and those in CR, received, as consolidation, either 2 courses of SDAC with 2 days of idarubicin (5–2–5)—very similar to the HiDAC induction cohort of our study—or 2 courses of SDAC with 3 days of idarubicin (5–3–5). This 50% increase in the dose of idarubicin resulted in a statistically improved OS and DFS due to a lower RR in that arm, suggesting that intensification of therapy over the standard protocol is necessary to improve the cure rate.

We can speculate that the optimal approach to maximize the chance of curing the patient of AML would be to administer >1 cycle of HiDAC-based chemotherapy—the initial as induction therapy, because of the greater chance of achieving CR—and if the patient is not planned to undergo alloHSCT in CR1, at least one additional cycle of HiDAC-based therapy as consolidation should be given—particularly for those patients with intermediate risk cytogenetics. Our study suffers from the usual limitations of retrospective studies and cannot definitively answer this question, only a well-designed, prospective, randomized study will be able to do this. Although we performed a careful comparison between the 2 cohorts of patients using propensity analyses, we cannot exclude that there were unmeasured or unknown variables present that have significantly affected the results. A particularly important deficit in our data is the lack of the very important mutational abnormalities (FLT3-ITD, NPM1, and others), which were not available for a majority of our patient cohort. Most, if not all AMLs, will have one or more mutations identified which are known to be important drivers of the leukemia, and which provide considerable prognostic information. We do not know if such mutational abnormalities were equally distributed between the 2 cohorts of our study.

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