High Risk of Relapse with Intermediate Dose Cytarabine for Consolidation in Young Favorable Risk AML Patients following Induction with 7+3

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INTRODUCTION

CALGB study in 1994 reported improved leukemia free survival (LFS) with sequential courses of high dose cytarabine (HIDAC- 3 gm/m^2, q12h on days 1, 3 and 5) compared to lower doses of 100 mg/m^2 and 400 mg/m^2 per day. Following this study, HIDAC has been commonly used for chemotherapy consolidation in AML patients 60 years or younger. More recently, several groups investigated the role of intermediate dose cytarabine (IDAC-1.5 gm/m^2 q12h D 1, 3 and 5 or D1-3) in this population and reported equivalent outcomes for IDAC compared to HIDAC (Table 1). ELN guidelines published in January 2017 recommend IDAC for consolidation therapy in young (<60 years) favorable risk AML patients. Following these studies and ELN publication, consolidation protocols for AML patients 60 years or younger were changed from HIDAC to IDAC at Singapore General Hospital (SGH) in 2011 and at University of Minnesota Medical Center (UMMC) in February 2017. NCCN continues to recommend HIDAC as category 1 recommendation for consolidation of patients in this setting.

OBJECTIVES

Compare outcomes in young favorable risk AML patients who received consolidation with HIDAC vs those who received consolidation with IDAC, following induction with 7+3.

METHODS

Patients 60 years or younger with ELN favorable risk AML between 2004 and 2015 at SGH and between September 2015 and March 2018 at UMMC, who underwent induction therapy with "7+3" regimen (idarubicin 12 mg/m^2 D1-3 or daunorubicin 60 – 90 mg/m^2 and cytarabine 100 mg/m^2 continuous infusion from D1-7) and consolidation with cytarabine monotherapy were identified. These dates were chosen to allow reasonably equal time distribution before and after change in our practice protocols. We extracted relevant demographic and outcomes data using chart review. We used Chi-square testing and applied Kaplan-Meier survival analysis to detect differences in outcomes of relapse and survival.

RESULTS

Of 67 ELN favorable risk patients 60 years or younger, 42 received HIDAC and 25 received IDAC. Median age was 39 years (range 16-59). 64 patients received 1 induction cycle and 3 patients received 2 induction cycles to achieve complete remission. Median LFS and overall survival (OS) with HIDAC vs IDAC were not-reached (NR) vs 1.35 years (p=0.004) and NR vs 2.27 years (p=0.001) respectively (Figure 1). Median time for follow up in HIDAC patients was 6.9 years. Cumulative incidence of relapse at 2 years was 23.8% for HIDAC and 60% for IDAC groups (p=0.003). 3-year LFS and OS for HIDAC vs IDAC groups were 71% vs 36% (p=0.06) and 90% vs 48% (p=0.002).

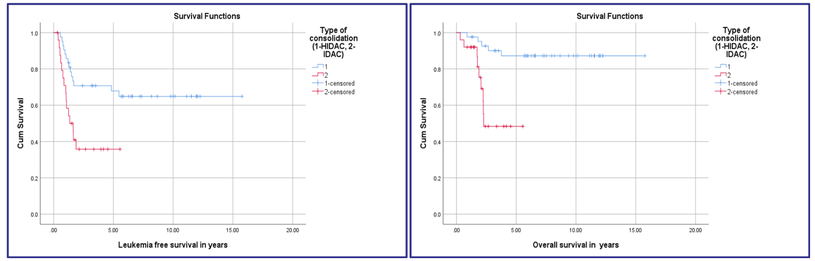

Figure 1. Kaplan-Meier curves for leukemia free survival and overall survival of patients who received consolidation with sequential cycles of HIDAC (blue line) vs IDAC (red line).

DISCUSSION

Historical data suggests chemotherapy consolidation with 3-4 sequential courses of HIDAC achieves long-term LFS of 60 – 70 % in young favorable risk AML patients. While the outcomes in HIDAC group in this study are comparable to historical data with good outcomes, a significantly larger proportion of patients in the IDAC group had early relapse (60%) and death. Data from large randomized studies in AML (Table 1) that suggest similar efficacy of IDAC compared to HIDAC used higher intensity induction regimens (frequently double induction therapy) compared to 7+3 and/or used other agents in combination with Ara-C for consolidation. These data are not broadly applicable in patients who receive a single cycle of 7+3 for induction for selecting dose of Ara-C as a monotherapy for consolidation. Furthermore, studies that used standard 7+3 for induction therapy showed benefit for HIDAC compared with multi-agent chemotherapy (Table 1).

CONCLUSIONS

Using single agent IDAC for post remission therapy is associated with higher rates of relapse and poor overall survival compared to HIDAC among young, ELN favorable risk AML patients who achieve CR following 7+3. The large randomized studies that suggested equivalency of IDAC to HIDAC for post remission therapy in AML patients, either used more than one cycle of intensive induction regimen and/or used cytarabine in combination with an anthracycline for consolidation. Hence, ELN guidelines should be cautiously interpreted given the above limitations in generalizability. Our study suggests that HIDAC, rather than IDAC, is the preferred chemotherapy consolidation regimen in young, favorable risk AML patients following standard 7+3 induction.

Disclosures: **Kolla:** *Amgen:* Equity ownership. **Weisdorf:** *Pharmacyclics:* Consultancy; *Incyte:* Research Funding; *Fate Therapeutics:* Consultancy.

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Study ID	Induction regimen(s) used	Consolidation regimens (comparator arms)	Results (specific to favorable risk category if available).	How these findings are applicable for post remission therapy of young favorable risk AML patients after 7+3
Studies suggesting IDAC = HIDAC for consolidation in AML				
Schaich et al. AML96 study. *J Clin Oncol 29:2696-2702. 2011*	Two cycles of induction therapy with MAV* followed by MAMAC*	I-MAC* vs H-MAC*. Additional cycle of MAMAC followed in good-risk patients.	No significant difference in 5-yr LFS (30% vs 33%) or 5-yr OS (37% vs 38%) between I-MAC vs H-MAC.	All patients received double induction, hence more intensive than 7+3. Mitoxantrone was included along with cytarabine in both I-MAC and H-MAC, thus comparison not limited between IDAC vs HIDAC. Additional cycle of MAMAC in good-risk patients, likely masking any differential impact of the comparator arms.
MRC AML15 Trial. Burnett AK et al. *J Clin Oncol 31:3360-3368. 2012*	Two cycles of induction therapy with one of three arms – ADE, DA or FLAG-Ida+.	2 cycles each of MRC regimen (MACE/MiDAC+) vs IDAC (cytarabine 1.5 g/m^2 q12h on d 1,3,5) vs HIDAC (cytarabine 3 g/m^2 q12h on d 1,3,5)	No significant difference in LFS or OS between MRC regimen and cytarabine group or between the two cytarabine groups (HIDAC vs IDAC).	Induction regimens were more intense than the 7+3 regimen. All patients received 2 cycles of induction before going to consolidation randomization. 2 courses of FLAG-Ida without further consolidation was equivalent to 4 courses of chemo in other arms. There was a trend for better OS with HIDAC compared to IDAC (HR 0.68) in favorable risk AML, numbers were few and did not reach statistical significance.
Studies suggesting HIDAC better than IDAC for consolidation in young favorable risk AML patients				
Miyawaki et al. JALSG AML201 Study. *Blood. 2011;117(8): 2366-2372.*	Ara-C 100 mg/m^2 7 days and either idarubicin (12 mg/m^2 for 3 days) or daunorubicin (50 mg/m^2) for 5 days.	HIDAC group, 3 courses of Ara-C 2 g/m^2 q12h for 5 days vs 4 courses of multi-agent chemotherapy+.	No significant difference in LFS and OS between the two groups in all patients. Significantly better 5-yr LFS in favorable cytogenetic group in patients receiving HIDAC for consolidation- 57% vs 39% (p=0.05)	Induction regimen was essentially comparable to 7+3 and was only single cycle. Compared consolidation with HIDAC vs multi-agent chemotherapy which included Ara-C dose of 1 g/m^2. Hence, not a head to head comparison between HIDAC vs IDAC. Results favored 3 cycles of HIDAC for consolidation in the favorable cytogenetic risk group vs multi-agent chemotherapy.
Kim et al. *Ann Hematol (2015) 94:1485–1492*	7+3 (Cytarabine 100 mg/m^2 D1-7 + Idarubicin 12 mg/m^2 D1-3)	3 or 4 cycles of HIDAC (cytarabine 3 g/m^2 q12h D1,3,5) Or AIDAC (cytarabine 1 g/m2 q12h on D1-3 + idarubicin or mitoxantrone 12 mg/m^2 on D 1-2)	Median OS and LFS in HIDAC were significantly longer than the AIDAC group (OS, NR vs 16.6 months, p=0.045; RFS 38.6 months vs 11 months, p=0.01)	Induction regimen was single cycle of 7+3. HIDAC significantly better than AIDAC that included anthracycline plus intermediate dose cytarabine.

Table 1. Summary of studies comparing HIDAC vs IDAC. **MAV** - Mitoxantrone 10 mg/m^2 on days 4 to 8, cytarabine 100 mg/m^2 continuous infusion on days 1 to 8, etoposide 100 mg/m^2 on days 4 to 8. **MAMAC** – Cytarabine 1000 mg/m^2, every 12 hours on days 1 to 5 [total dose of 10 g/m^2], amsacrine 100 mg/m^2 on days 1 to 5. **I-MAC** – Cytarabine 1 g/m^2 every 12 hours on days 1 to 6 (total dose of 12 g/m^2) and mitoxantrone 10 mg/m^2 on days 4 to 6. **H-MAC** - Cytarabine 3 g/m^2 every 12 hours on days 1 to 6 (total dose of 36 g/m^2) and mitoxantrone 10 mg/m^2 on days 4 to 6. + - Please refer to the manuscript for the regimens and doses.

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