INTRODUCTION

CALGB study in 1994 reported improved leukemia free survival (LFS) with sequential courses of high dose cytarabine (HIDAC-3 g/m², q12h on days 1, 3, and 5) compared to lower doses of 100 mg/m² and 400 mg/m² 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 g/m² D 1, 3 and 5 or D1-3) in this population and reported equivalent outcomes for HIDAC compared to IDAC (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 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

To 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/m² D1-3 or daunorubicin 6–90 mg/m² and cytarabine 100 mg/m² continuous infusion from D1-8) and this setting.

This setting.

More recently, several groups investigated the role of intermediate induction therapy with “7+3” regimen (idarubicin 12 mg/m² D1-3 or daunorubicin 60–90 mg/m² and cytarabine (IDAC-1.5 g/m² q12h D 1, 3 and 5 or D1-3) in this population and between SGH and between September 2015 and March 2018 at UMMC, who underwent induction therapy showed benefit for HIDAC compared with multi-agent 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).

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 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

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

Bhaskar Kolla, NAA Halim, Qing Cao, Zohar Sachs, Erica Warlick, Daniel Weisdorf, William Hwang, Fiona He, Zhentang Lao

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

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).

DISCUSSION

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

Bhaskar Kolla, NAA Halim, Qing Cao, Zohar Sachs, Erica Warlick, Daniel Weisdorf, William Hwang, Fiona He, Zhentang Lao

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, guidelines should 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.

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).

Table 1. Summary of studies comparing HIDAC vs IDAC. MAV - Mitoxantrone 10 mg/m² on days 4 to 8, cytarabine 100 mg/m² continuous infusion on days 1 to 8, and daunorubicin 45 mg/m² on days 1 to 3. MAMAC - Mitoxantrone 1000 mg/m² divided into four courses of 250 mg/m² every 12 hours on days 1 to 5 [total dose of 10 g/m²], mitoxantrone 100 mg/m² on days 1 to 5. MACE - Cytarabine 1 g/m² every 12 hours on days 1 to 5 (total dose of 12 g/m²) and mitoxantrone 10 mg/m² on days 6 to 8. H-MAC - Cytarabine 3 g/m² every 12 hours on days 1 to 6 (total dose of 36 g/m²) and mitoxantrone 10 mg/m² on days 1 to 8. + Please refer to the manuscript for the regimens and doses.

Table 1. Summary of studies comparing HIDAC vs IDAC. MAV - Mitoxantrone 10 mg/m² on days 4 to 8, cytarabine 100 mg/m² continuous infusion on days 1 to 8, and daunorubicin 45 mg/m² on days 1 to 3. MAMAC - Mitoxantrone 1000 mg/m² divided into four courses of 250 mg/m² every 12 hours on days 1 to 5 [total dose of 10 g/m²], mitoxantrone 100 mg/m² on days 1 to 5. MACE - Cytarabine 1 g/m² every 12 hours on days 1 to 5 (total dose of 12 g/m²) and mitoxantrone 10 mg/m² on days 6 to 8. H-MAC - Cytarabine 3 g/m² every 12 hours on days 1 to 6 (total dose of 36 g/m²) and mitoxantrone 10 mg/m² on days 1 to 8. + Please refer to the manuscript for the regimens and doses.

Contact: Bhaskar Kolla. Email: bckolla@umn.edu