Further Evidence to Not Delay Transplant for Continued ARA-C Consolidation in Patients with Intermediate or High Risk AML

Oklahoma ACP Scientific Meeting

September 12, 2015

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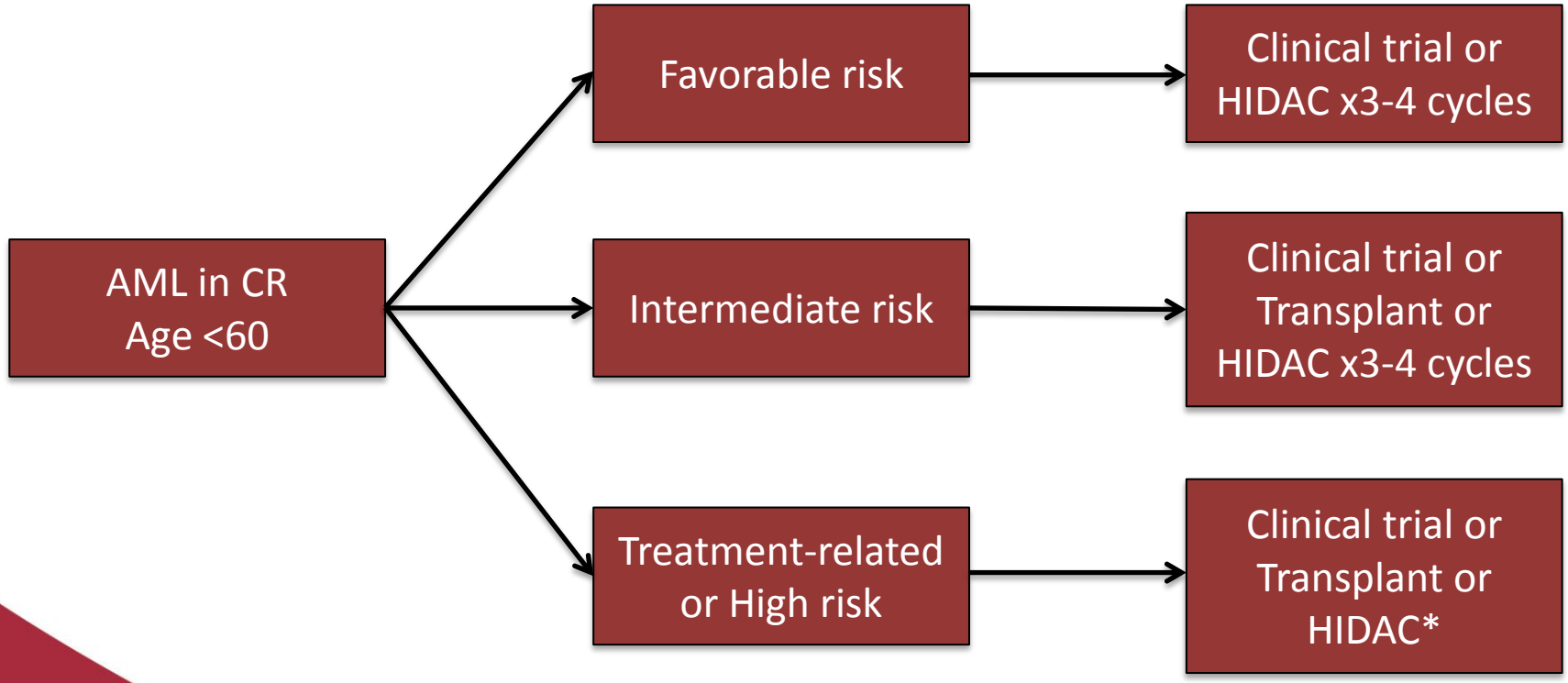
The University of Oklahoma

Background: *Fork In The Road*

Once a patient with acute myeloid leukemia has achieved a complete remission (CR), what is the next step?

http://www.capitolvolkssportclub.org/cvc_specialevents/millersylvania_2012_se.html

Background: *Fork In The Road*



Margaret O, Martin T, et al. Acute Myeloid Leukemia Version 1.2015. *NCCN Clinical Practice Guidelines in Oncology*. 2015. Available at: http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed August 18, 2015.

Background: *Fork In The Road*

Risk Status	Cytogenetics	Molecular Abnormalities
Favorable	Core binding factor: inv(16), t(16;16), or t(8;21) t(15;17)	Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD or isolated biallelic CEBPA mutation
Intermediate	Normal cytogenetics +8 alone t(9;11) Other non-defined	t(8;21), inv(16), t(8;21): with c-KIT mutation
Poor	Complex (≥3 abnormalities) Monosomal Karyotype 11q23 – non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)	Normal cytogenetics: with FLT3-ITD mutation

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Research Question

- Does additional Ara-C treatment given before allogeneic stem cell transplant confer a post-transplant survival benefit for patients who undergo full myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC)?
  - Well established benefit of HIDAC vs. IDAC or standard-dose cytarabine[2]
  - Reduction of undetectable leukemic burden before transplant could reduce relapse post transplant
  - Not all patients are ready for transplant immediately after CR
- Previous reports suggest no additional benefit[3-6]
  - Most studies done in patients who underwent RIC transplant preparative regimen

Methods

- Appropriate IRB approval was obtained in accordance with the Helsinki Declaration (IRB # 4965)
- Retrospective chart review in all adult patients with AML who underwent allogeneic SCT at our center from October 2006 to October 2014 (n = 71)
  - Patients under age 18 or over age 60 were excluded (n = 6)

Methods

- Data collected:
  - Demographic data
  - Date of diagnosis
  - Cytogenetic/molecular risk status
  - All pre-transplant chemotherapy given
  - Transplant preparative regimen
  - Status at transplant
  - Date of transplant
  - Date of relapse at any time
  - Date of death or last clinic visit (censored 6/30/2015)

Methods

- BMT Pharmacist reviewed chemo history of each patient and calculated cumulative pre-transplant dose of Ara-C
- Statistical analysis
  - Simple descriptive statistics were created for all covariates [mean, SD for continuous covariates and n (%) for categorical variables].
  - A Cox proportional hazards model was used to assess the association of each covariate with overall survival (OS).

Table 1A: Simple Descriptive Statistics Continuous Variables

Variable	Min	Max	Mean	SD
Age (years)	18.0	59.0	42.8	12.5
Ara-C (g/m^2)	0.7	127.4	43.8	31.2
Diagnosis to SCT (days)	65	2531	362	447

Table 1B: Simple Descriptive Statistics Categorical Variables

Variable	n (%)
Race	
White	57 (87.7)
Non-White	8 (12.3)
Risk	
Favorable	7 (10.8)
Intermediate	37 (56.9)
Unfavorable	19 (29.2)
Unknown	2 (3.1)
Cell Type	
BMT	28 (45.2)
CORD	8 (12.9)
PBSCT	26 (41.9)

Variable	n (%)
Prep Type	
Full	44 (67.7)
RIC	21 (32.3)
Status Pre-transplant	
CR1	36 (58.1)
CR2 & CR3	26 (41.9)

Table 2: Survival Analysis Results from Multivariable Model

Variable	HR (95% CI)	p-value
Ara- C	0.99 (0.97-1.00)	0.0633
Age	1.037 (1.00 – 1.07)	0.0364
Risk		
Favorable (ref)	-	-
Intermediate	2.45 (0.31 -19.2)	0.3922
Unfavorable	8.94 (1.14 – 69.9)	0.0368

Note that none of the other continuous variables in table 1A or the other categorical variables in table 1B were found to be statistically significant.

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Results

- Status at transplant: CR1 vs. CR 2/3
  - HR = 1.25 (95% CI 0.65 – 2.39 p = 0.5033).
  - There is also no statistical significance when comparing CR1, CR2, and CR3 individually
- Time to transplant
  - HR = 0.999 (95% CI 0.998-1.00, p-value = 0.0480)
  - Not significant in multivariable model
- Transplant preparative regimen: RIC vs MAC
  - HR = 0.51 (95% CI 0.26-0.99 p=0.0467)
  - Not significant in multivariable model

Results

- Logistic regression results predicting relapse in a multivariate model
  - Ara-C OR 0.99 (95% CI 0.97-1.00, p=0.2558)
  - No other variable had $p < 0.25$

Conclusions

- Prior studies suggest that further ARA-C therapy given during consolidation does not correlate with improved outcomes post-transplant in patients with AML who received a reduced intensity preparative regimen; we attempted to expand this data to further include patients who received a full myeloablative preparative regimen.
- Our experience suggests further ARA-C therapy given in consolidation does not benefit patients who underwent either RIC or MAC prep regimens in terms of post-transplant survival.

Conclusions

- Our experience confirms that AML patients with intermediate and high risk disease should proceed to transplant without delay, provided a suitable donor is identified.

Acknowledgements

- Faculty:
  - **Mohamad Khawandanah MD**
  - **Mohamad Cherry MD**
  - Jennifer Holter-Chakrabarty MD
  - Carrie Yuen MD
  - George Selby MD
- Fellow:
  - Nicholas Pleat DO
- Pharmacy:
  - Sara Schmidt PharmD
- Biostatistics:
  - Michael Machiorlatti MS
  - Summer Frank MPH
  - Sara Vesley PhD

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Questions

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