Analysis Concept Proposal

Title: Long-term outcomes among survivors of childhood acute myeloid leukemia
Working Groups: Chronic Disease, Second Malignancy, Biostatistics

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Background and Rationale:
Acute myeloid leukemia (AML) is the 2nd most common pediatric leukemia. Over the course of the last 4 decades 5-year overall survival has increased from <30% in the 1970s[1] to 64% in the current treatment era.[2] Treatment has evolved during this time course, progressing from remission induction followed by a prolonged maintenance course in the 1970s and early 1980s, to more dose-intensive, shorter duration regimens in the early 1980s. Allogeneic hematopoietic cell transplantation (HCT) became more widely recommended beginning in the 1980s, and post-induction intensification with high-dose cytarabine and daunorubicin became a standard component of therapy in the mid-1990s. These therapeutic modifications have led to improvements in survival due to decreased relapse,[3] but survival improvements are also attributable to decreased treatment related mortality secondary to improvements in supportive care.[4] Nevertheless, there is concern that more recent survivors may have a greater burden of late effects due to treatment intensification.

The CCSS has recently published comprehensive reports on overall survivor late mortality[5], subsequent neoplasms (SNs)[6], and health status.[7] An analysis of global chronic conditions is currently under review[8]. Despite compelling decreases among the CCSS cohort, as a whole, in late mortality[5], serious chronic diseases[8], and SNs[6], and no improvement in self-reported health status[7], results specific to AML survivors have not been reported in detail. There are a limited number of reports describing the late health consequences specifically among long-term AML survivors, and the impact of therapeutic changes over time are not fully described. The most recent comprehensive examination of AML survivors from the CCSS cohort (limited to those diagnosed between 1970-1986) was published in 2008 and examined survival and relapse rates, late mortality, late medical complications and socioeconomic factors among survivors of AML not treated with HCT.[9] Twenty-year cumulative incidence of subsequent malignant neoplasms (SMNs) was 1.7% and of cardiac events was 4.7%. Risk for serious chronic conditions was significantly increased compared with sibling controls.[9] There has not been a detailed examination of health outcomes among CCSS AML survivors treated in more recent treatment eras (through 1999) or for CCSS AML survivors treated with HCT.

Analyses of late effects specific to survivors of AML have been published from other groups over the last two decades. Leung et al. detailed late effects of a cohort of 77 10-year survivors of AML treated at St. Jude Children's Research Hospital between 1976-1989, including treatment with chemotherapy only, chemotherapy+cranial radiation, and chemotherapy+total body irradiation (TBI)+allogeneic HCT.[10]

They found frequent occurrence of late effects, including abnormalities in growth, neurocognition, endocrine and cardiac function, as well as cataracts, with increased risk for endocrinopathies and cataracts secondary to treatment with TBI and HCT. Cumulative incidence of subsequent malignant neoplasms (SMNs) was 1.8% at 20 years after diagnosis.[10] The Nordic Society of Pediatric Hematology and Oncology (NOPHO) has reported on multiple long-term outcomes among 137 survivors of AML treated with chemotherapy only on the protocols between 1984 and 2003.[11-14] Self-reported health status was similar among survivors compared to siblings, with more frequent use of prescription drugs but no increase in hospitalizations compared to siblings.[12] Most of the group showed normal pubertal development and fertility at a median follow-up of 11 years,[13] and renal, gastrointestinal and hepatic late effects were rare.[14] Compared to controls, left ventricular functions was reduced, but most survivors still had cardiac function within normal limits.[11] Chronic health conditions, quality of life and health behaviors following chemotherapy ± autologous or allogeneic HCT among a small population of AML survivors treated between 1979 and 1995 were addressed in analyses by the Children's Oncology Group[15,16] Allogeneic HCT recipients were more likely to report multiple and severe chronic health conditions, and overall very few of the COG AML survivors reported cancer-related pain, anxiety or sadness/suicidality and health-related quality of life was similar to the general population.[15,16] Chronic conditions among a small population of AML and myelodysplastic syndrome survivors (N=62) from the Children's Hospital of Philadelphia treated 1970-1994 with chemotherapy or allogeneic HCT were reported nearly 20 years ago.[17] Overall, chronic health conditions were observed at a low frequency in both the chemotherapy and HCT groups, with similar incidence between the groups for each of the assessed conditions with the exception of higher need for estrogen supplementation in the HCT group compared to the chemotherapy group.

With this study, we will have the opportunity to examine the long-term health outcomes among 866 5-year survivors of childhood AML diagnosed between 1970 and 1999 and will further address whether there have been temporal changes in these outcomes. Given that most AML survivors are not exposed to radiation, that use of high-dose cytarabine became more standard in the late 1980s, and that increasing numbers are being treated with HCT in more recent years, we hypothesize that there will not be significant treatment-associated temporal improvements in late mortality or health outcomes, and furthermore, among individuals treated with HCT, long-term health outcomes may be inferior compared with those without HCT. We will address these hypotheses through the following specific aims:

Specific Aims and Hypotheses:

1. Quantify mortality rates in long-term survivors of AML.
   a. Estimate cumulative incidence of mortality by decade of diagnosis and HCT status (yes/no, as available) and calculate standardized mortality ratios, using US population data, to compare changes over time.
   b. Compare cumulative incidence of mortality to other CCSS survivors by decade of diagnosis.
   c. Describe causes of death, by decade of diagnosis, and estimate cumulative incidence of cause-specific death by decade of diagnosis.
   d. Use piecewise exponential models to estimate the impact of temporal changes in therapeutic exposures on standardized mortality ratios (SMRs). Specifically, for therapeutic exposures, we will examine the influence of HCT vs. not, and also outcomes among those treated with chemotherapy regimens similar to contemporary AML treatments (further described in the Analytic framework).
   Hypothesis: Rates of late mortality will not be significantly different based on decade of diagnosis, but will be greater among HCT recipients compared to AML survivors treated with chemotherapy only.

2. Describe late health consequences in long-term survivors of AML, including overall chronic conditions, cardiac, pulmonary, renal, hepatic and endocrine complications and SNs.
   a. Estimate the cumulative incidence of overall chronic health conditions (grades 1-5 and 3-5) by decade of diagnosis and HCT status and compare changes over time and compare with siblings.

b. Examine cumulative incidence of cardiac, pulmonary, renal, hepatic and endocrine conditions (grades 1-5 and 3-5) and SNs, as well as SIRs of SNs, by decade of diagnosis and compare changes over time.
c. Perform regression analyses to assess associations between treatment exposures and chronic conditions.
Hypothesis: Rates of chronic conditions will be increased over time (with the exception of SNs, which will be stable) and will be highest among HCT recipients compared to recipients of chemotherapy only, and will be increased for the group as a whole compared to siblings and/or the general population. We further anticipate recipients of HDAC will experience higher rates of chronic conditions compared to those not receiving HDAC.

3. Compare poor health status outcomes among long-term survivors of AML, including general health, mental health, physical activity limitation, functional impairment, and cancer-related pain and anxiety.
   a. Quantify the proportion of AML survivors, by decade of diagnosis, experiencing the outcomes above. Compare differences based on decade of diagnosis and HCT status and compare to siblings.
   b. Use multivariable models to estimate the impact of temporal changes in therapeutic exposures on health status outcomes.
   Hypothesis: The health status of survivors will be similar across decades of diagnosis and will be worse in HCT survivors compared to survivors treated with chemotherapy only. Health status measures will be inferior compared to siblings.

Analysis Framework:

a. Population of interest: This analysis will include survivors enrolled in the CCSS cohort, diagnosed 1970-1999, who had an initial cancer diagnosis of AML (N=866) and who were treated with a) chemotherapy only, or b) chemotherapy and HCT. Siblings of all CCSS survivors will be included as a comparison group.
b. Descriptive characteristics of the AML cohort:
   1. Age at diagnosis, sex, race, childhood malignancy, attained age, time from initial diagnosis, decade of diagnosis (1970s, 80s, 90s)
   2. Environmental/lifestyle exposures: smoking status (yes [ever smoked]/no), alcohol use (yes/no/average drinks per week)
   3. Down syndrome (yes/no/unknown)
   4. Therapeutic exposures
      1. Therapeutic radiation
         a. Yes/No
         b. TBI Yes/No
         c. Cranial radiation Yes/No
         d. Maximum dose to exposed body region
      2. Chemotherapy protocol, agent class and cumulative doses
         a. Chemotherapy protocol (if documented on the MRAF)
         b. Alkylating agents (yes/no/cumulative dose, reported as cyclophosphamide equivalent dose [18])
         c. Anthracyclines (yes/no/cumulative dose, reported as doxorubicin equivalent dose)
         d. Epipodophyllotoxins (yes/no/cumulative dose)
      3. Following the example of prior CCSS analyses[19] (Oeffinger et al. Hodgkin concept 15-07, not yet published), we also will attempt to create comparison groups that approximate the exposure profile of contemporary AML protocols (see Supplemental Table for agents/doses). It is recognized that this may be somewhat exploratory in nature since the

MRC-based regimens were not widely used in the U.S. until the mid-to-late 1990s and the CCSS has not collected cytarabine cumulative dosing for the expansion cohort.

a. MRC-based therapy with cytarabine, daunorubicin, ±etoposide, mitoxantrone, asparaginase
b. DCTER (CCG)-based therapy with dexamethasone, cytarabine, thioguanine, etoposide, daunorubicin/idarubicin
c. Any HDAC-containing regimen (POG 9194, 9421, CCG 213, 213P, 2941, 2961, St. Jude AML 87, 91, 97; will review cumulative dosing when available and other protocols for inclusion as well)

4. Hematopoietic cell transplantation (full details available for 1987-99; will use previous methods to identify HCT for 1970-86 [may not be able to differentiate auto and allo])
   a. Autologous Yes/No
   b. Allogeneic Yes/No

c. Mortality analysis variables
   i. Vital status (alive/dead), based on most recent National Death Index update
   ii. If dead, age at death
   iii. Underlying cause of death, based on death certificates. Will use categories which mirror those used by Armstrong et al.[5]
      1. Recurrence/progression of primary malignancy (AML)
      2. External cause (i.e. accidents, injuries, suicide)
      3. Non-recurrence, non-external cause (chronic health conditions)
         a. SMN cause
         b. Cardiac cause
         c. Pulmonary cause
         d. Other
d. Chronic health conditions variables
   i. Overall chronic health conditions, consider any Common Terminology Criteria for Adverse Events (CTCAE, version 4), grade (1-5) and severe or life-threatening (grades 3-5)
   ii. Cardiac conditions, consider any CTCAE grade (1-5) and severe or life-threatening (grades 3-5)
   iii. Pulmonary conditions, consider any CTCAE grade (1-5) and severe or life-threatening (grades 3-5)
   iv. Renal conditions, consider any CTCAE grade (1-5) and severe or life-threatening (grades 3-5)
   v. Hepatic conditions, consider any CTCAE grade (1-5) and severe or life-threatening (grades 3-5)
   vi. Endocrine conditions, consider any CTCAE grade (1-5) and severe or life-threatening (grades 3-5)
   vii. Subsequent neoplasms (SNs)
      1. Subsequent malignant neoplasms (SMNs, ICD-O, 5th digit =3)
      2. Non-melanoma skin cancers (NMSCs)
      3. Non-malignant meningiomas
e. Health status variables (based on work by Ness et al[7])
   i. General health: reported answer to “Would you say that your health is: excellent, very good, good, fair or poor” (Original N15, Expansion O21)
   ii. Mental health: based on subscale (depression, anxiety, somatization) scores of the Brief Symptom Inventory (BSI) (Original J16-35, Expansion K1-18)
   iii. Activity limitations: (Original N14 b,c,e, Expansion O20 b,c,e)
   iv. Functional impairment (Original N10-12, Expansion O16-18)
   v. Cancer related pain (Original J36 Expansion K19)
   vi. Cancer related anxiety (Original J37, Expansion K20)

Statistical approach:
Mortality: Cumulative incidence of mortality will be estimated for overall group, by decade of diagnosis and based on HCT status. We will report cumulative incidence for each of the mortality categories described above, accounting for competing risk of death from other causes. Standardized mortality ratios (SMRs) will be calculated for the group as a whole and by decade of diagnosis, considering all cause and cause specific mortality. Expected number of deaths will be calculated using age- and sex-specific mortality rates for the U.S. population from the National Center for Health Statistics. Multivariable Poisson regression will be performed to adjust for the effect of multiple factors on SMR and piecewise exponential analysis will be performed to look at the impact of demographic factors, treatment era, and treatment exposures (including treatment on DCTR-based protocols vs. MRC-based protocols +/- HCT) on mortality rates.

Chronic health conditions: We will estimate the cumulative incidence of 1) grade 1-5, 2) grade 3-5 conditions (overall and by organ system), and 3) SNs (overall and by subtype) overall, by decade of diagnosis, by chemotherapy regimen, and by HCT status. Deaths due to causes other than chronic conditions or SNs will be considered as competing risks. Comparisons between survivors will be made based on decade of diagnosis, HCT status and survivors will also be compared to siblings. For organ systems with sufficient numbers of events, we will estimate cumulative incidence of specific conditions and assess changes by decade of diagnosis. We will calculate standardized incidence ratios (SIRs) for SMNs, using age, sex, race/ethnicity and calendar year U.S. cancer rates from SEER to evaluate expected number of events. SIRs will be reported by decade of diagnosis and by HCT status. Cox regression models, allowing for the possibility of multiple events, will be used to estimate hazard ratios and to compare risk across treatment decades, adjusting for demographics and treatment variables. For SMNs, piecewise exponential modelling will be used to compare SIRs. Since patients with Down syndrome are likely to be overrepresented in the AML survivor population and they are likely to experience an increased number of chronic conditions (cardiac, endocrine), in part because of their underlying chromosomal disorder, we will repeat the chronic condition analyses without Down syndrome survivors to understand the impact of this syndrome on these outcomes.

Health status: Participants (survivors and siblings) will be classified as having poor general health if they responded Poor or Fair to general health question. Poor mental health will be defined as a score $\geq$63 on any of the 3 BSI subscales. Activity limitation will be defined as answering more than three months to any of the three questions. Participants who answer Yes to any of the three functional impairment questions will be considered to have a functional impairment. Survivors (siblings not assessed for cancer related pain or anxiety) who endorse a lot, very bad excruciating pain, or medium amount of pain will be classified as having cancer-related pain, and those who answer a lot, very many/extreme, or medium amount of anxiety/fears will be classified as having cancer-related anxiety. Using these classifications, the prevalence of each health status outcome outlined above will be calculated and survivors will be compared to siblings when applicable. We will compare prevalence estimates based on decade of diagnosis and HCT status. Multivariable log-binomial models will be used to understand how treatment variables, decade of diagnosis, chronic health conditions and demographics are associated with prevalence of health status outcomes, with results reported as prevalence ratios (PR).

Proposed Tables and Figures:

Table. AML survivor characteristics.

	Overall N=	Treated with chemotherapy only N=	Treated with chemotherapy and HCT N=	CCG-based treatment N=	MRC-based treatment N=
Mean age at primary diagnosis, years					
Sex Male Female					
Race/ethnicity White Black Hispanic Other Unknown					
Decade of diagnosis 1970-79 1980-89 1990-99					
Chemotherapy Anthracycline (mg/m2) None 0-100 101-300 >300 Epipodophyllotoxin (mg/m2) None 1-1000 1001-4000 >4000 Alkylating agent (CED) (mg/m2) None 1-3999 4000-7999 8000+					
Radiation None Cranial radiation Total body irradiation Other radiation site Maximum radiation dose to any body region (Gy)					
Hematopoietic cell transplantation None Autologous Allogeneic					
Vital status Alive Deceased					
Survival after diagnosis (years) 5-9 10-14 15-19 20-24 25-29 30-34 ≥35					
Number of person-years since cohort entry					
Mean years of follow up from diagnosis, years					

Table. Causes of death, by decade of diagnosis and HCT status

	1970-79						1980-89					
Cause of death	Overall	SMR	Chemo only	SMR	HCT	SMR	Overall	SMR	Chemo only	SMR	HCT	SMR
Recurrence/progression												
External causes												
Non-recurrence, non-external causes												
SMN												
Cardiac												
Pulmonary												
Other												

	1990-99					
Cause of death	Overall	SMR	Chemo only	SMR	HCT	SMR
Recurrence/progression						
External causes						
Non-recurrence, non-external causes						
SMN						
Cardiac						
Pulmonary						
Other						

Table. Causes of death, by chemotherapy regimen

Cause of death	Overall	SMR	CCG-based	SMR	MRC-based	SMR	Any HDAC	SMR
Recurrence/progression								
External causes								
Non-recurrence, non-external causes								
SMN								
Cardiac								
Pulmonary								
Other								

Table. Relative SMRs of death from health-related causes and the effect of treatment exposure per 5- (or 10-) year treatment era, according to multivariable model

	Overall	Chemo only	HCT
No adjustment for therapy			
Remove: Anthracycline Alkylating agent Epipodophyllotoxin Radiation			

**In this model, can also examine whether chemotherapy regimens (CCG-based or MRC-based) impact relative rates

Table. Cumulative incidence (15 years?) of any grade 1-5 chronic health conditions by HCT status, by decade of diagnosis. (Will also look at Cardiac, Pulmonary, Hepatic, Renal and Endocrine specifically)

	1970-79			1980-89			1990-99			*P*
	At risk	Cum Inc	95% CI	At risk	Cum Inc	95% CI	At risk	Cum Inc	95% CI	
Overall										
Chemo only										
HCT										

Table. Cumulative incidence (15 years?) of any grade 3-5 chronic health conditions by HCT status, by decade of diagnosis. (Will also look at Cardiac, Pulmonary, Hepatic, Renal and Endocrine specifically)

	1970-79			1980-89			1990-99			*P*
Treatment group	At risk	Cum Inc	95% CI	At risk	Cum Inc	95% CI	At risk	Cum Inc	95% CI	
Overall										
Chemo only										
HCT										

Table. Relative risk of select grade 3-5 chronic health conditions overall and by system, by decade of diagnosis. (can also look at same based on HCT status instead of decade of diagnosis)

	1970-79			1980-89			1990-99			*P*
	Survivor N=	Sibling N=	RR (95% CI)	Survivor N=	Sibling N=	RR (95% CI)	Survivor N=	Sibling N=	RR (95% CI)	
All conditions										
Cardiac										
Pulmonary										
Renal										
Hepatic										
Endocrine										
SMN*										
Other										

*Will examine relative SIRs for SMNs.

Table. Relative risk of a chronic health condition, according to treatment and decade of diagnosis, as compared with siblings.*

	Grade 1-5	Grade 3-5	>/= 2 conditions	SMN
Siblings	1.0	1.0	1.0	1.0
Chemo Any chemo Alkylating agent Anthracycline Epipodophyllotoxins CCG-based regimen MRC-based regimen HDAC regimen				
Radiation therapy None Cranial XRT TBI Other				
HCT None Auto Allo				
Decade of diagnosis 1970-79 1980-89 1990-99				

*Each row adjusted for attained age, sex, race/ethnicity. (maybe others as appropriate)

Table. Proportion of AML survivors and siblings experiencing adverse health status outcomes, by decade of diagnosis.

	1970-79				1980-89				1990-99			
	Overall N=	Chemo N=	HCT N=	Sib N=	Overall N=	Chemo N=	HCT N=	Sib N=	Overall N=	Chemo N=	HCT N=	Sib N=
Poor general health												
Poor mental health												
Activity limitation												
Functional impairment												
Cancer-associated pain												
Cancer-associated anxiety												

Table. Prevalence Ratios for adverse health status outcomes among AML survivors, by decade of diagnosis, treatment and demographics. (add other lifestyle variables? Smoking, drinking, etc)

	Poor general health		Poor mental health		Activity limitation		Functional impairment		Cancer-associated pain		Cancer-associated anxiety	
	Survivor %	PR (95 % CI)	Survivor, %	PR (95 % CI)	Survivor, %	PR (95 % CI)	Survivor, %	PR (95 % CI)	Survivor, %	PR (95 % CI)	Survivor, %	PR (95 % CI)
Chemo Any chemo Alkylator Anthracyc Epipodoph.												
Radiation therapy None CranialXRT TBI Other												
HCT None Auto Allo												
Chemo regimen CCG-based MRC-based HDAC												
Decade of diagnosis 1970-79 1980-89 1990-99												

*Each row adjusted for attained age, sex, race/ethnicity. (maybe others as appropriate)

Figures:

1. Cumulative incidence curves of mortality (consider comparison to other CCSS survivors, for reference)
    a. By decade of diagnosis
    b. By HCT status
    c. By CCG-based vs. MRC-based therapy
    d. By any HDAC vs. not
    e. By cause of mortality
2. Cumulative incidence and cumulative burden (mean cumulative count) curves of chronic conditions
    a. Overall group, all conditions, grades 1-5 and grades 3-5
    b. By HCT status, all conditions, grades 1-5 and grades 3-5
    c. By CCG-based vs. MRC-based therapy
    d. By decade of diagnosis, all conditions, grades 1-5 and grades 3-5
    e. By chronic condition group (endocrine, cardiac), grades 1-5 and grades 3-5 (can consider specific conditions if numbers permit)
3. Cumulative incidence and cumulative burden (mean cumulative count) curves of SNs
    a. Overall group: SMNs, NMSC and non-malignant meningiomas
    b. HCT group: SMNs, NMSC, and non-malignant meningiomas
    c. Chemo only group: SMNs, NMSC and non-malignant meningiomas
    d. CCG-based therapy: SMNs, NMSC and non-malignant meningiomas
    e. MRC-based therapy: SMNs, NMSC and non-malignant meningiomas
    f. Any HDAC: SMNs, NMSC and non-malignant meningiomas
    f. SMNs by decade of diagnosis
    g. NMSC by decade of diagnosis
    h. Non-malignant meningiomas, by decade of diagnosis
4. SIRs for SMNs, by attained age and decade of initial AML diagnosis (similar to Turcotte et al Figure 3[6]), can consider looking at HCT vs. chemo only (or by chemotherapy regimen).

Supplemental Table

CCG-based*	CCSS Eligible Dose Range	MRC-based^	CCSS Eligible Dose Range
Induction (1st 2 cycles)		**Induction (1st 2 cycles)**	
Dexamethasone 96 mg/m2	Any	Daunorubicin 300 mg/m2	300±75 mg/m2
Cytarabine 3.2 g/m2	3.2±0.8 g/m2	Cytarabine 3.6 g/m2	3.6±0.9 g/m2
6-thioguanine (6TG) 1600mg/m2	Any	Etoposide 1000 mg/m2	1000±250 mg/m2
Etoposide 1600mg/m2	1600±400 mg/m2		^ADE only, *no* dexamethasone or 6TG
Daunorubicin 320 mg/m2	320±80 mg/m2		
	* CCG-based must include any dexamethasone and 6TG + ADE		
Post-Induction (if not BMT)		**Post-Induction**	
1. Capizzi II Cytarabine 24g/m2 L-asparaginase 12,000IU/m2	 24±6 g/m2 Any	**1. MACE** Amsacrine 500 mg/m2 Cytarabine 1000 mg/m2 Etoposide 500 mg/m2	 Any 1000±250 mg/m2 500±125 mg/m2
2. ATCO x2 6TG 4200 mg/m2 Vincristine 3mg/m2 Cytarabine 600 mg/m2 Cyclophosphamide 600 mg/m2	 Any Any 600±150 mg/m2 600±150 mg/m2	**3. MidAC** Mitoxantrone 50 mg/m2 Cytarabine 5g/m2	 50±12.5mg/m2 5±1.25 g/m2
4. DENVER Etoposide 600 mg/m2 Daunorubicin 30 mg/m2 Cytarabine 500 mg/m2	 600±150 mg/m2 30±7.5 mg/m2 500±125 mg/m2		

6TG 500 mg/m2 Dexamethasone 8 mg/m2	Any Any		
*****Post-Induction use of L-asparaginase or vincristine may further define CCG-based therapy		^Post-Induction use of amsacrine or mitoxantrone may further define MRC-based therapy	

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