05-06

Childhood Cancer Survivor Study
Analysis Concept Proposal

Title: Long-Term Survivors of Childhood Acute Myeloid Leukemia

Working Group: Chronic Disease Working Group

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Background and Rationale:

Survival rates for children diagnosed and treated for acute myeloid leukemia have improved, although at a slower rate than for lymphoid leukemia. This improvement can be credited to national treatment protocols and improvements in supportive care, such as newer and better directed antibiotic therapy, hospitalization during aplasia, and the use of G-CSF. Organized study and clinical trials of childhood AML through both the Pediatric Oncology Group and Children's Cancer Group, and now the combined Children's Oncology Group, have greatly advanced therapy and survival for this challenging childhood illness.

Numerous trials have helped advance induction and post-remission therapy for pediatric AML. Various combinations of non-cross resistant chemotherapeutic agents and timing of these drugs have been studied. The "7&3" regimens, combination with the "Denver" regimen (Ara-C, daunomycin, dexamethasone, etoposide, and 6-thioguanine), timing of sequential remission induction therapy, and the role of stem cell transplant and donor source in consolidation have all contributed to gradual improvements in survival.[1-7]

Through these sequential clinical investigations overall survival from pediatric AML has neared 50%. However, despite this improvement the medical literature contains only a few small studies concerning the late effects, both medical and psychosocial, experienced by this group of very aggressively treated childhood cancer survivors.[8-10]

Specific Aims/Objectives/Research Hypotheses:

This study will use data from the Childhood Cancer Survivor Study (CCSS) to determine survival rates, rates of relapse, late mortality, late medical complications, and socioeconomic (education, marriage, employment, insurance) factors in survivors of childhood AML not treated with stem cell transplant.

Hypotheses:

1) Overall and event-free survival will be significantly lower among survivors of childhood AML compared to the general U.S. population.

2) Survivors of childhood AML therapy will experience significant late morbidity compared with a sibling control group and population norms (i.e. early cardiovascular disease, endocrine disorders, second cancers, etc.)

3) Survivors of childhood AML will be less educated, and less likely to be employed, have insurance coverage, or be married than the sibling control group and the general population.

Analysis Framework:

A. Outcomes of interest:
   1. Survival rates
   2. Medical Complications:
      a. Baseline: medical conditions, sections C,D,E, F, G, H, I, J
      b. Follow-up 1: medical conditions, questions: 9, 10, 11, 12
   3. Second Cancers:
      a. Baseline: section K
      b. Follow-up 1: question 17
      c. Follow-up 2: section R
   4. Education:
      a. Baseline: section O, questions 1-4
      b. Follow-up 1: question 1
      c. Follow-up 2: question 1
   5. Employment:
      a. Baseline: section O, questions 5-11, section Q, questions 8, 9
      b. Follow-up 2: question 3
      c. Follow-up 3: questions 4, 5, 6
   6. Insurance:
      a. Baseline: section Q, questions 1-6
      b. Follow-up1: question 16
      c. Follow-up 2: section M
   7. Marriage:
      a. Baseline: section L

b. Follow-up 1: question 2
c. Follow-up 2: questions 2 and 3

8. Pregnancy history:
    a. Baseline: section M
    b. Follow-up 1: question 8
    c. Follow-up 2: section N

B. Subject population:

1. all de novo AML survivors in the CCSS cohort who have survived 10 years from diagnosis, (estimated at 362 in the CCSS cohort, ICD-0 codes attached)
2. eligible siblings, frequency matched 3:1 to cases, on gender, age (5 year age groups), and race
3. U.S. Census Bureau data
4. Medical Expenditure Panel Survey data

C. Explanatory variables:

1. Age at cancer diagnosis
2. Age at response to CCSS questionnaire
3. Gender
4. CNS involvement
5. Type of treatment (chemotherapy, CNS radiation)
6. Type and cumulative doses of chemotherapy
7. CNS radiation doses

D. Analysis Plan:

1. Descriptive Epidemiology/Summary statistics:
    a. Characteristics of AML survivors will be described using means (SD) or medians (range).

2. Survival Analysis:
    a. Overall survival and event-free survival will be analyzed from the 5^{th} and 10^{th} anniversary dates of event-free survival with the life table method (Kaplan-Meier curves).
    b. Hazard ratios comparing survival between the different groups will be evaluated using Cox proportional hazards regression models adjusted for age at diagnosis, gender, race, and treatment era.
    c. Standardized mortality ratios (observed number of deaths divided by the expected number) and their 95% confidence intervals will be calculated by the Breslow and Day method.
    d. Cumulative incidence of relapse, SMN, and death during remission will be calculated, treating death prior to the event of interest or relapse, as appropriate, as competing risk events. Hazard ratios for these outcomes comparing the different groups will be calculated with Cox proportional hazards regression adjusted for age at diagnosis, gender, race, and treatment era.

3. The chi-square test of independence (or Fisher's exact test if expected frequencies are less than 5) will be used to compare proportions of medical complications, educational levels, employment status, insured status, marital status of cases, siblings, and the general population.

4. Multiple logistic regression, log linear regression, or Poisson regression will be used to compare rates of medical complications, educational levels, employment status, insured status, marital status of cases, siblings, and the general population.

E. Tables and Figures:

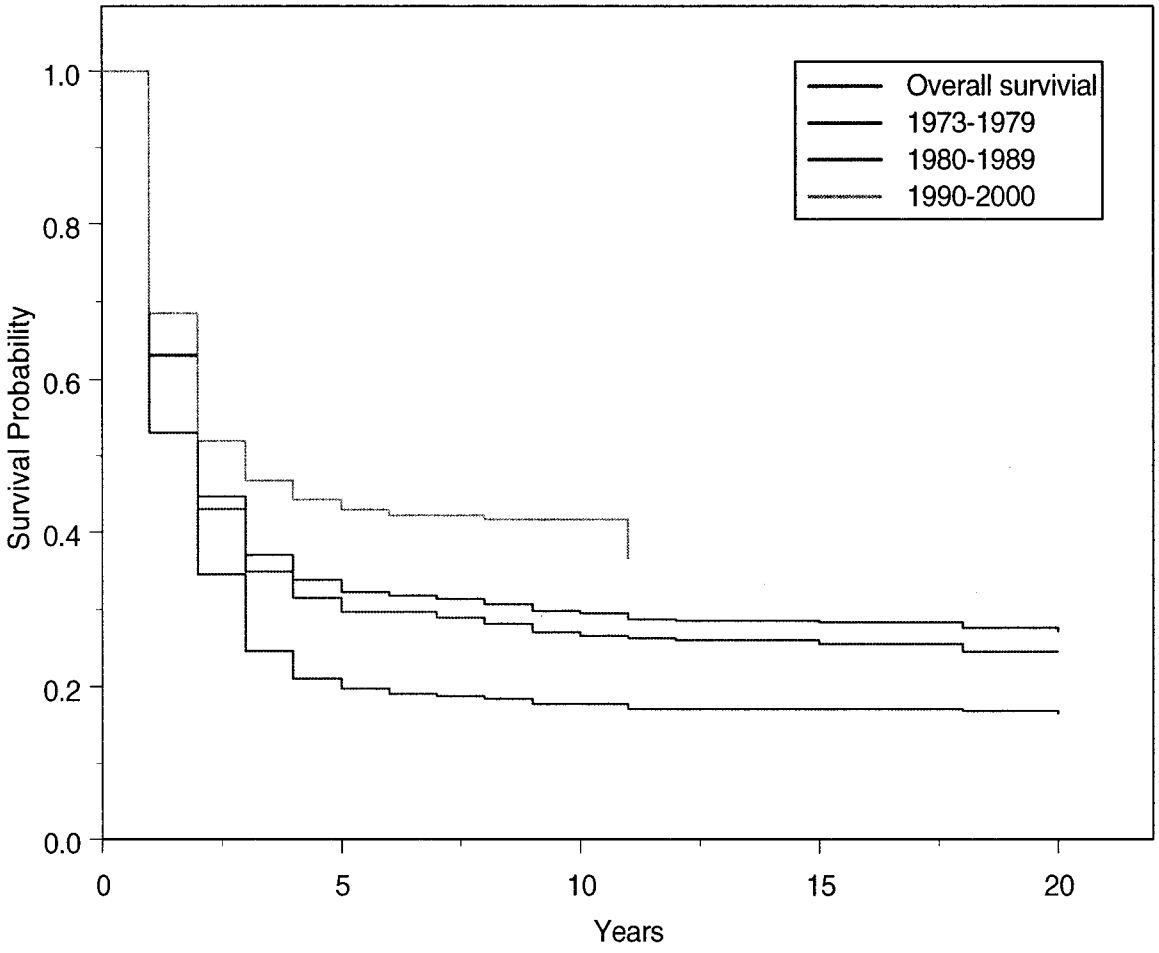
1. Demographic table of CCSS AML cases:
    - sex
    - diagnosis
    - age at diagnosis
    - age at follow-up
    - treatment
    - treatment era
    - medical complications

2. Survival curves: overall survival, event free survival
3. Cumulative incidence curves: late medical outcomes, second cancers
4. Tables: educational attainment, employment status, insurance status, marital/family status demonstrating frequencies and rates of each of these social indicators compared to the sibling control group and population norms

Special Consideration:

This concept proposal is submitted in response to the CCSS steering committee's request for disease-focused initiatives within the CCSS cohort.

Estimated overall survival of pediatric AML patients by treatment era (SEER Data)



Estimated number of AML survivors participating in the CCSS study

Count	leukemia diagnosis
3	9840.3 Erythroleukemia
4	9860.3 Myeloid leukemia, NOS
211	9861.3 Acute myeloid leukemia
14	9864.3 Aleukemic myeloid leukemia
22	9866.3 Acute promyelocytic leukemia
55	9867.3 Acute myelomonocytic leukemia
1	9880.3 Eosinophilic leukemia
39	9891.3 Acute monocytic leukemia
3	9894.3 Aleukemic monocytic leukemia
9	9910.3 Acute megakaryoblastic leukemia
1	9930.3 Myeloid sarcoma

References

1. Loeb DM, Arceci RJ: What is the Optimal Therapy for Childhood AML? Oncology 16:1057-1066, 2002

2. Buckley JD, Lampkin B, Nesbit ME, et al: Remission Induction in Children with Acute Nonlymphocytic Leukemia Using Cytosine Arabinoside and Doxorubicin or Daunorubicin. Med Pediatri Oncol 17:382-390, 1989

3. Nesbit ME, Buckley JD, Feig SA, et al: Chemotherapy for Induction of Remission of Childhood Acute Myeloid Leukemia Followed by Marrow Transplantation or Multigent Chemotherapy: A Report From the Children's Cancer Group. J Clin Oncol 12:127-135, 1994

4. Woods WG, Kobrinsky N, Buckley JD et al: Intensively Timed Induction Therapy Followed by Autologous or Allogeneic Bone Marrow Transplantation for Children with Acute Myeloid Leukemia or Myelodysplastic Syndrome: A Children's Cancer Group Pilot Study. J Clin Oncol 11:1448-1457, 1993

5. Wells RJ, Woods WG, Lampkin BC, et al: Impact of High-Dose Cytarabine and Asparaginase Intensification on Childhood Acute Myeloid Leukemia: A Report from the Children's Cancer Group. J Clin Oncol 11:538-545, 1993

6. Woods WG, Neudorf S, Gold A et al:A Comparison of Allogeneic Bone Marrow Transplantation, Autologous Bone Marrow Transplantation, and Aggressive Chemotherapy in Children with Acute Myeloid Leukemia in Remission: a Report from the Children's Cancer Group. Blood 97:56-62, 2001

7. Lang BJ, Dinndorf P, Smith FO, et al: Pilot Study of Idarubicin-Based Intensive-Timing Induction Therapy for Children with Previously Untreated Acute Myeloid Leukemia: Children's Cancer Group Study 2941. J Clin Oncol 22:150-156, 2004

8. Leung W, Hudson MM, Strickland DK, et al: Late Effects of Treatment in Survivors of Childhood Acute Myeloid Leukemia. J Clin Oncol 18:3273-3279, 2000

9. Redaelli A, Stephens JM, Brandt S, et al: Short and Long-Term effects of Acute Myeloid Leukemia On Patient Health-Related Quality of Life. Cancer Treatment Reviews 30:103-17, 2004

10. Michel G, Socie G, Gebhard F, et al: Late Effects of Allogeneic Bone Marrow Transplantation for Children with Acute Myeloblastic Leukemia in First Complete Remission: The Impact of Conditioning Regimen without Total-Body Irradiation – A Report from the Societe Francaise de Greffe de Moelle. J Clin Oncol 15:2238-2246, 1997

Table 1. Characteristics of the study population

	AML Survivors (N=X)		Siblings (N=X)		
	N	(%)	N	(%)	p-value
Gender					
Female					
Male					
Age at diagnosis					
Mean (SD)					
0-4 years			N/A		
5-9 years			N/A		
10-14 years			N/A		
15+ years			N/A		
Age at questionnaire					
Mean (SD)					
18-29 years					
30-39 years					
40-49 years					
50+ years					
Survival time					
Mean (SD)					
15-19 years					
20-24 years					
25-29 years					
30+ years					
Highest level of education					
Grade school					
High school					
Technical school					
College					
Post graduate					
Not indicated					
Marital status					
Married or living as married					
Not married					
Not indicated					
Employment status					
Working full time					
Not working full time					
CNS involvement			N/A		
Yes					
No					
CNS prophylaxis			N/A		
IT chemotherapy					
CNS directed RT					

Table 2. Frequencies, percents, odds ratios and 95% CIs comparing AML survivors and siblings on medical complications*

	AML				Siblings			
	N	%	OR	95% CI	N	%	OR	95% CI
Medical complications								
Relapse								
No								
Yes								
SMN								
No								
Yes								
Cardiovascular								
Congestive heart failure								
No								
Yes								
Ischemic Heart Disease								
No								
Yes								
Endocrine								
Hypothyroid								
No								
Yes								
Infertility								
No								
Yes								
Pulmonary								
No								
Yes								
Neurosensory								
Vision								
Hearing								
Abnormal sensation								
Pain								

* Adjusted for age at interview

Table 3. Rates of socioeconomic factors in AML survivors compared to siblings and the general population*

Married			Separated or Divorced			Never Married		
Cases	Siblings	Population	Cases	Siblings	Population	Cases	Siblings	Population
% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Employment Status								
Fulltime			Part-time			Unemployed		
% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Education								
No High School Education			High School Graduate			Post High School Education		
% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Insurance								
Private Insurance			Public Insurance			No Insurance		
% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)

* Adjusted for gender and age at interview
† Case rate differs from sibling rate ($p<0.05$)
‡ Case rate differs from population rate ($p<0.05$)