INCIDENCE AND CLINICAL RELEVANCE OF ABNORMAL

COMPLETE BLOOD COUNTS IN SURVIVORS OF CHILDHOOD CANCER

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INCIDENCE AND CLINICAL RELEVANCE OF ABNORMAL COMPLETE BLOOD COUNTS IN SURVIVORS OF CHILDHOOD CANCER

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ABSTRACT

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Background: The purpose of this study was to determine the incidence and clinical significance of abnormal complete blood counts (CBCs) obtained during follow-up of childhood cancer survivors.

Methods: A retrospective cohort study was conducted on 193 survivors, diagnosed between 1970-1986, who have been followed in our center's After Cancer Experience Program and are participants in the Childhood Cancer Survivor Study. Of these patients, 49% were female and 25% were racial/ethnic minorities. The primary outcome was determination of the cumulative percentage of patients having an abnormal CBC by 2 or 3 standard deviations (SDs). Four components of the CBC were examined and employed to define an abnormal CBC: low white blood cell count (WBC), high mean corpuscular volume (MCV), low platelet count, and low hemoglobin concentration. Association of treatment exposures to abnormal values was assessed with a multi-level logistic model.

Results: There were 1,376 patient visits during 1,437 person-years of follow-up. The mean number of visits per survivor was 7.2 (SD 4.5). The cumulative percentage of subjects with at least one abnormal CBC was 70%. The cumulative percent of subjects with a value abnormal by 2 SD was WBC=23%, MCV=33%, platelets=9%, hemoglobin=49%. For values abnormal by 3 SD, the frequencies were WBC=3%, MCV=18%, platelets=1%, hemoglobin=27%. None of the patients developed myelodysplastic syndrome or a secondary leukemia during the follow-up period. Exposure to epipodophyllotoxins was associated with an increased risk of having abnormally high MCV values.

Conclusions: Mildly abnormal CBC values are common in survivors of childhood cancer. Abnormal values are often of questionable significance but seem to persist over time. Epipodophyllotoxin therapy was found to be associated with increased frequency of high MCV levels.

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PRIOR PUBLICATIONS AND PRESENTATIONS

In Review:

2005 "Incidence and clinical relevance of abnormal complete blood counts in long-term survivors of childhood cancer". Long ZB, Oeffinger, KC, Fischbach L, Harris TR, Brooks SL, Eshelman DA, Tomlinson GE, Buchanan GR. *Cancer*

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2003 "Incidence and clinical relevance of abnormal complete blood counts in long-term survivors of childhood cancer" Long ZB, Oeffinger, KC, Fischbach L, Brooks SL, Eshelman DA, Tomlinson GE, Buchanan GR. Poster presentation at the at the 41st Medical Student Research Forum, UTSW Medical School, Dallas, TX

2002 "Incidence of Abnormal Complete Blood Counts of Childhood Cancer Survivors in Long-term Follow-up" Long ZB, Oeffinger, KC. Seminar at the Department of Family Practice and Community Medicine, UTSW Medical School, Dallas, TX

2000 "Partial Amplification and Cloning of a Beta Carbonic Anhydrase in *Arabidopsis thaliana*" Long ZB, Bartlett SG. Seminar as partial fulfillment of the requirements for graduation from the Honors College at Louisiana State University, Baton Rouge, LA

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LIST OF ABBREVIATIONS

ACE – After Cancer Experience

AML – acute myelocytic leukemia

CBC – complete blood count

CCSS – Childhood Cancer Survivor Study

CNS – central nervous system

CI – confidence interval

G-CSF – granulocyte colony-stimulating factor

MCV – mean corpuscular volume

MDS – myelodysplastic syndrome

PY – person-year

RR – relative risk

SD – standard deviation

t-AML – treatment related acute myelocytic leukemia

t-MDS – treatment related myelodysplastic syndrome

WBC – white blood cell

CHAPTER I

Introduction

With improved treatment of childhood cancer, a new and growing generation of adolescents and young adults is in need of surveillance for late effects caused by their cancer therapy. Virtually all organ systems can be affected by cytotoxic therapy.[1,2] Childhood cancer survivors are frequently followed in long-term follow-up programs and are periodically screened for late effects of therapy. Testing is based upon treatment exposures.

Potential serious sequelae that may affect survivors are treatment-related leukemia (t-AML) or myelodysplastic syndrome (MDS). The median latency period for the development of t-AML is 5-7 years following treatment with alkylating agents,[3,4] and 2-3 years after exposure to topoisomerase II inhibitors.[4-6] Alkylating agent exposure is often found among Hodgkin disease survivors,[3,7] whereas epipodophyllotoxin therapy has been used for the treatment of acute lymphocytic leukemia.[5,8] A peripheral blood count abnormality is often the presenting manifestation for t-AML/t-MDS.[9-12]

The recently published "Children's Oncology Group (COG) Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers" recommend an annual CBC with platelet and differential white blood cell (WBC) count for 10 years following diagnosis for patients treated with epipodophyllotoxins and anthracyclines, and for 15 years for patients exposed to alkylating agents.[13] The stated rationale for testing is to screen for secondary hematologic alterations. The optimal duration of such surveillance is not known. No

prior studies on childhood cancer survivors specifically examined CBCs for alterations that might suggest evolving t- AML/t-MDS or marrow injury from cumulative effects of chemotherapy and radiation. Therefore, this study was conducted retrospectively to determine the incidence and clinical significance of abnormal CBCs obtained during the extended follow-up of a cohort of childhood cancer survivors.

CHAPTER II

Methods

Between 1970-86, 483 patients were diagnosed with cancer and were subsequently long-term survivors at Children's Medical Center Dallas, with the following eligibility criteria: a) diagnosis with one of eight cancer groups (leukemia, Hodgkin disease, non-Hodgkin lymphoma, central nervous system tumor, soft tissue sarcoma, Wilms tumor, neuroblastoma, bone cancer); b) survival of 5 years or more from date of diagnosis; and c) age less than 21 at diagnosis. Of this population, 299 (62%) were enrolled on the Childhood Cancer Survivor Study (CCSS). Of the remaining 184 patients, 128 (27%) were lost to follow-up, 52 (11%) refused participation, and 4 (1%) died prior to enrollment, one of whom developed t-AML. Of the 299 patients enrolled in CCSS, 193 (65%) were seen at least once in a clinical setting in the After Cancer Experience (ACE) Program at Children's Medical Center Dallas or at the University of Texas Southwestern Medical Center at Dallas, TX. In this retrospective cohort study, all available laboratory data and clinical information were reviewed on these 193 patients. Complete blood count values that were obtained at least two years after completion of cancer treatment were recorded. The data collection ended in August 2002. The demographic information on our subjects is summarized in Table 1.

Table 1. Demographics of 193 childhood cancer survivors

Abbreviations: SD, standard deviation..

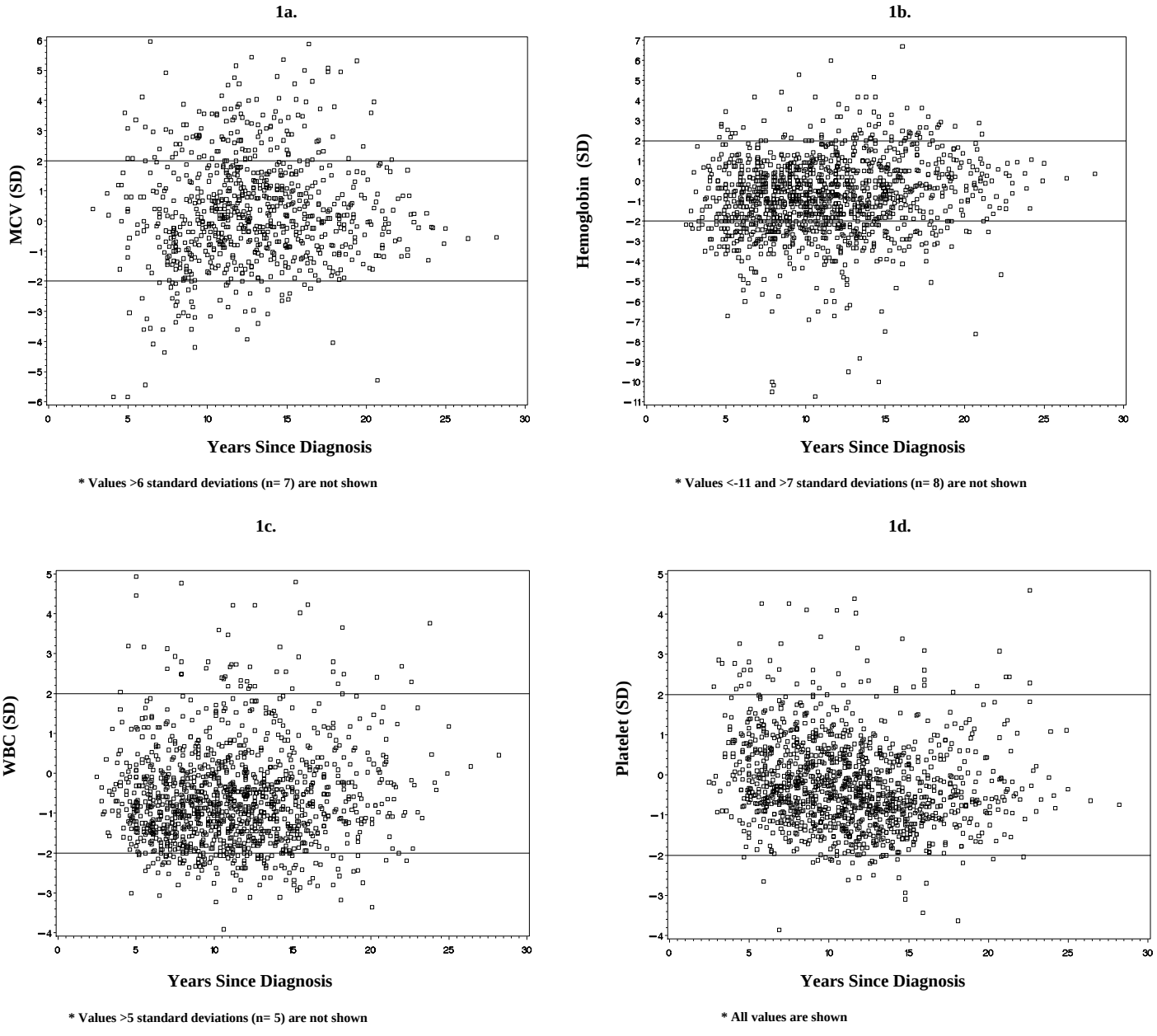
Variables	N	%
Gender		
Female	95	49.2
Male	98	50.8
Race		
White	145	75.1
African American	26	13.5
Hispanic	19	9.8
Other	3	1.6
Cancer diagnosis		
Leukemia	102	52.9
Central nervous system tumor	4	2.1
Hodgkin disease	11	5.7
Non-Hodgkin lymphoma	8	4.2
Wilms tumor	36	18.7
Neuroblastoma	19	9.8
Soft tissue sarcoma	10	5.2
Bone tumor	3	1.6
Cancer treatment		
Alkylating agent	100	62.5
Epipodophyllotoxin	26	16.3
Anthracycline	80	50.0
Radiation, any site	82	48.8
Age at cancer diagnosis (Yr)		
Mean (SD)	4.8 (3.9)	
Median	3.7	
Range	0.0 - 16.4	
Age at last visit (Yr)		
Mean (SD)	19.7 (5.2)	
Median	19.2	
Range	7.8 – 34.5	
Interval from diagnosis to last visit (Yr)		
Mean (SD)	15.0 (4.5)	
Median	14.9	
Range	4.0 - 28.4	

Note: Percentages are based upon the total with available data for each variable.

For each blood count, the normal range provided on the laboratory report was recorded. For missing normal range values, age-, and gender-specific normal range values were substituted. By definition, the normal range encompassed up to plus or minus 2 standard deviations (SD) from the average for that value in a normal population of the same age and gender. For the purposes of this study, an abnormal blood count was defined as follows: > ± 2SD from the mean value, which corresponds to being outside the normal range for a given laboratory value, and > ± 3SD from the mean, a value being slightly more abnormal. The incidence of abnormal laboratory values was calculated for four blood count measures felt to indicate bone marrow injury, including low WBC count, low hemoglobin concentration, low platelet count, and high erythrocyte mean corpuscular volume (MCV).

Scatter plots were created with the y-axis representing the number of standard deviations from the mean for each of the blood count measure of interest and the x-axis the time from diagnosis to the visit (Figure 1a-d).

Figure 1. Standard deviation of MCV (1a), hemoglobin (1b), WBC (1c), and platelet (1d) values by years from diagnosis for 1,376 patient visits.
Each square represents a visit at which the particular blood count measure was obtained in any patient. The two horizontal lines represent + and – 2SD with the interval in between representing the normal range for that laboratory value. Abbreviations: MCV, mean corpuscular volume; SD, standard deviation; WBC, white blood cell count.



Univariate analysis was performed to assess the association of abnormal CBCs with different cancer treatments, gender, age at diagnosis, and race. A multi-level logistic model was constructed, which incorporated the repeated measures within individuals, to further investigate the relationship of cancer treatments, length of time from diagnosis, and total number of visits to the likelihood of obtaining a high MCV, or low hemoglobin, WBC, and platelet count.[14] Total chemotherapy doses were divided into tertiles to investigate whether increasing doses of chemotherapy were associated with increased likelihood of having an abnormal laboratory value. The lowest tertile was compared to not having received that particular agent. The multi-level logistic model was used to account for the differences between the numbers of visits among individuals, and therefore patients who were seen more frequently were not over-represented in the analysis. The model was adjusted for age at diagnosis, race, and gender.

Data were analyzed with SAS v9.0 (SAS Institute, Cary, NC) and MLWIN software. This study was approved by University of Texas Southwestern Medical Center Institutional Review Board.

CHAPTER III

Results

The mean number of visits during which at least one component of the CBC was performed was 7.2 (SD= 4.5, range 1-21) with a mean interval from cancer diagnosis to the last follow-up visit of 15.0 years (SD= 4.5, range 4.0-28.4). The total follow-up period was 1,437 person-years (PY). The mean age at last follow-up visit was 19.7 years (SD=5.2, range 7.8-34.5). None of the subjects developed t-MDS/t-AML, or aplastic anemia. Two patients died from non-hematologic causes.

Figure 1 represents scatter-plots of standard deviation of MCV (1a), hemoglobin (1b), WBC (1c), and platelet (1d) values by years from diagnosis for 1,376 patient visits. Table 2 summarizes the prevalence of abnormal laboratory results (> ± 2SD and > ± 3SD) per person. The expected percentage of at least one abnormal laboratory value for an average of 7.2 visits of follow-up was calculated based on the properties of normal distribution. For any abnormally high or low value > ± 2SD from the mean the expected percentage is 16.7% (1-0.975^7.2), and for > ± 3SD from the mean the expected percentage is 3.5% (1-0.995^7.2). Of note, the prevalence of having one or more abnormal values of interest > ± 2SD was 69.9%, and > ± 3SD from the mean was 40.4%. The prevalence of abnormal laboratory values > ± 2SD for each of the blood counts per 1000 person-years (PY) was 30.6 for low WBC, 43.8 for high MCV, 12.5 for low platelet counts, and 66.1 for low hemoglobin. The prevalence of abnormal laboratory values > ± 3SD per 1000 PY was 4.2 for low WBC, 23.7 for high MCV, 1.4 for low platelet counts, and 36.2 for low hemoglobin.

Table 2. Frequency of abnormal CBC values (> ± 2SD and > ± 3SD) per person

For each blood count measure the found and expected percentages of abnormal values are shown. The expected percentages were calculated for an average of 7.2 visits (range 1-21). The second and third columns show abnormal values > ± 2SD, the fourth and fifth columns show values > ± 3SD.

Abbreviations: CBC, complete blood count; MCV, mean corpuscular volume; PY, person-years; SD, standard deviation; WBC, white blood cell count.

Blood count measure	Percentage of patients with abnormal values (> ± 2SD)	Expected frequency of abnormal values (> ± 2SD) in a normal population	Percentage of patients with abnormal values (>± 3SD)	Expected frequency of abnormal values (> ± 3SD) in a normal population
Low WBC	22.8%	16.7%	9.8%	3.5%
High MCV	32.6%	16.7%	17.6%	3.5%
Low platelet	9.3%	16.7%	1.0%	3.5%
Low hemoglobin	49.2%	16.7%	26.9%	3.5%

Estimates of relative risk (RR) and 95% confidence intervals for the multi-level analysis are provided in Table 3. Participants who received epipodophyllotoxins were more likely to have an abnormally high MCV during follow-up. Each dose range increase in epipodophyllotoxin was associated with a 60% increase in risk for high MCV (95% CI =1.1-2.3). Anthracyclines and alkylating agents were not significantly associated with any of the abnormal CBC values. Participants who had radiation treatment were less likely to have low hemoglobin concentrations (RR= 0.4; 95% CI=0.2-0.8) and low platelet counts (RR= 0.2; 95% CI=0.0-0.9). Increasing time from diagnosis to follow-up was associated with a lower likelihood of having a high MCV value (RR=0.9; 95% CI=0.9-1.0). Increasing time from diagnosis to follow-up was also associated with a lower likelihood of having a low hemoglobin concentration (RR=0.9; 95% CI= 0.9-1.0). Increased number of follow-up visits was related to increased risk for low hemoglobin (RR=1.1; 95% CI=1.0-1.2). Black race was associated with increased risk of low hemoglobin (RR= 7.2; 95% CI= 2.8-18.2) and low WBC count (RR= 4.2; 95% CI= 1.4-12.9). Of note, no difference was found in males and females in the frequency of abnormal hemoglobin concentration. Seventeen survivors (9%) had a low hemoglobin value and a low MCV at the same visit.

Table 4 lists patients with one or more markedly abnormal CBC values, as well as their demographic information and co-morbid conditions that may have contributed to their abnormal blood counts.

Table 3. Multi-level logistic model with relative risk estimates (RR) and 95% confidence intervals (95% CI) of the likelihood of having abnormal (>± 2SD) blood values for 193 patients having 1,376 visits.[*]

The first column shows the independent variables including three increasing dose ranges of anthracyclines, alkylating agents, and epipodophyllotoxins; radiation, time since diagnosis, total number of visits. The effects of these independent variables on the likelihood of obtaining an abnormally high MCV, low hemoglobin, low WBC, and low platelet count are expressed as relative risks. Significant findings include confidence intervals excluding "1.0" and P-values < 0.05. Abbreviations: CI, confidence interval; MCV, mean corpuscular volume; NA, not applicable; RR, relative risk; WBC, white blood cell count; Yr, year.

	High MCV			Low Hemoglobin			Low WBC			Low Platelet Count		
Independent Variables	**RR**	**95% CI**	***P*-value**	**RR**	**95% CI**	***P*-value**	**RR**	**95% CI**	***P*-value**	**RR**	**95% CI**	***P*-value**
Anthracycline Dose[**]	0.7	0.5 - 1.0	0.07	1.3	1.0 - 1.8	0.10	0.8	0.5 - 1.2	0.27	0.9	0.5 - 1.8	0.86
Epipodophyllotoxin Dose[**]	1.6	1.1 - 2.3	0.02	0.9	0.6 - 1.3	0.50	1.0	0.6 - 1.7	0.91	0.9	0.4 - 2.1	0.81
Alkylating Dose[**]	1.5	1.0 - 2.2	0.08	1.0	0.7 - 1.4	0.86	1.2	0.8 - 1.9	0.43	1.9	0.9 - 4.1	0.09
Radiation (Yes vs. No)	1.9	0.9 - 4.1	0.08	0.4	0.2 - 0.8	0.006	0.7	0.3 - 1.5	0.36	0.2	0.0 - 0.9	0.04
Time since diagnosis (Yr)	0.9	0.9 - 1.0	0.04	0.9	0.9 - 1.0	<.0001	1.0	0.9 - 1.1	0.81	1.1	1.0 -1.2	0.16
Total number of visits	1.0	0.9 - 1.1	1.0	1.1	1.0 - 1.2	0.01	1.0	1.0 - 1.1	0.39	1.1	0.9 -1.3	0.30

* Adjusted for age at diagnosis, age, and gender.

** Chemotherapy dosing was categorized as none, lowest dose range, medium dose range, and highest dose range.

Table 4. Demographics, co-morbid conditions, and laboratory values of patient visits with a markedly abnormal value

For most markedly abnormal laboratory values there are co-morbid conditions affecting the patient that could account for the blood count abnormalities.
Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; B, black; CA, carcinoma; EBV, Epstein-Barr virus; ESRD, end-stage renal disease; d/o, disorder; F, female; Fe, iron; H, Hispanic; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HTN, hypertension; HD, Hodgkin disease; ITP, idiopathic thrombocytopenic purpura; M, male; MCV, mean corpuscular volume; NA, not available; tx, therapy; Yr, year; W, white;WAGR, Wilms tumor, aniridia, genitourinary malformations, mental retardation; WBC, white blood cell count.

Abnormality	Patient	WBC (K/mm^3)	Hemoglobin (g/dl)	MCV (μm^3)	Platelet count (K/mm^3)	Gender	Primary Diagnosis	Age at visit (Yr)	Race	Comorbid Conditions
WBC $\geq$ 30 K/mm^3	1	36	14	82	321	F	ALL	20	W	Current EBV infection
WBC $\leq$ 2.5 K/mm^3	2*	1	8	NA	137	F	HD	23	B	Fe deficiency
	3	2	12	88	162	F	ALL	11	H	Seizure d/o, Depakote tx, Fe deficiency
	4	2	14	NA	229	M	Wilms tumor	21	B	None
	5	2	12	NA	505	M	Neuroblastoma	6	H	None
MCV $\geq$ 110 μm^3	6	7	17	114	108	M	ALL	19	W	Down's, Cyanotic heart disease
	6	3	22	115	98	M	ALL	20	W	Down's, Cyanotic heart disease
Hemoglobin $\leq$ 9 g/dl	2*	1	8	NA	137	F	HD	23	B	Fe deficiency
	7	10	8	61	367	F	Neuroblastoma	22	B	History of Fe deficiency, pica
	3	3	9	70	251	F	ALL	19	H	Seizure d/o, Depakote tx, Fe deficiency
	8	16	8	84	232	M	AML	17	B	ESRD, renal cell CA at age 20, HBV
	8	12	9	83	321	M	AML	17	B	ESRD, renal cell CA at age 20, HBV
	8	10	8	84	302	M	AML	20	B	ESRD, renal cell CA at age 20, HBV
	8	13	8	85	468	M	AML	20	B	ESRD, renal cell CA at age 20, HBV
	8	11	7	84	378	M	AML	20	B	ESRD, renal cell CA at age 20, HBV
	8	8	7	84	331	M	AML	20	B	ESRD, renal cell CA at age 20, HBV
Platelet count $\leq$ 100 K/mm^3	9	4	11	85	80	M	Wilms tumor	16	W	WAGR
	6	3	22	115	98	M	ALL	20	W	Down's, Cyanotic heart disease
	10	5	16	98	68	M	ALL	21	H	Down's, HBV, portal HTN, hypersplenism
	10	5	15	103	43	M	ALL	22	H	Down's, HBV, portal HTN, hypersplenism
	10	4	14	106	28	Male	ALL	25	H	Down's, HBV, portal HTN, hypersplenism
	11	4	15	NA	11	Male	HD	20	W	HIV, ITP

* Subject 2 had a significantly abnormal hemoglobin and low WBC at the same visit

CHAPTER IV

Discussion

This study is the first to report blood count results obtained over an extended period of follow up in childhood cancer survivors. Among 193 survivors followed for an average of 15 years after cancer diagnosis, 70% had at least one abnormality of the four CBC measures examined. Thus, abnormal CBCs were common in this population, possibly reflecting bone marrow injury. Assuming a normal distribution and an average of 7.2 visits per person, the expected frequency of an abnormally high or low value (i.e. > ± 2SD from the mean) is 17%. In this cohort the actual frequency of low WBC was 23%, high MCV was 33%, and low hemoglobin was 49% compared to the expected 17% value.

Many investigations have described the increased risk of developing secondary leukemia after treatment for childhood malignancies.[15-19] The risk of t-AML varies according to cancer treatment, age at diagnosis, length of follow-up, among other contributing factors. The ten-year cumulative incidence of t-AML ranges from 0.7% to 4.2%.[9,20,21] Two major types of t-AML have been described. The first type arises after treatment with alkylating agent therapy, with a median latency period of approximately 6.6 years.[3,4] Cytogenetic analysis in these individuals often reveals deletional aberrations of chromosomes 5 or 7. The overt leukemia of this type is heralded by preleukemic changes of 6 or more months duration in the majority of the patients.[10,11] It has been suggested that identifying and treating patients in the preleukemic phase may halt their progression to t-AML.[22] The second type of t-AML occurs after therapy with topoisomerase II inhibitors, which often shows a

characteristic translocation involving the 11q23 band.[5,6,23,24] The median latency period is only 2-3 years,[4-6] much shorter than that of the alkylator induced t-AML. Epipodophyllotoxin related t-AML is not preceded by observable preleukemic changes. In both types of t-AML the presentation of patients differs from the presentation of individuals with *de novo* AML, including lower white blood cell (WBC) counts.[25]

If a preleukemic phase is present, peripheral blood counts may reveal pancytopenia, anemia or erythrocyte macrocytosis, or involvement of two cell lines such as thrombocytopenia with anemia or leukopenia.[10,11] Such abnormalities are often initially minimal or subtle. Overt leukemia presents with circulating erythroblasts, anisocytosis, basophilic stippling, granulocytopenia, or granulocyte hypogranularity, and basophilia, in addition to the abnormalities found in the preleukemic stage.[9,10,12]

Only a few studies have investigated peripheral blood count abnormalities of otherwise healthy survivors during follow-up. One analysis of 73 survivors of childhood Ewing sarcoma reported a higher incidence of t-AML in those treated with higher dose chemotherapy (including large doses of alkylating agents, topoisomerase II inhibitors, and granulocyte colony-stimulating factor (G-CSF)) in comparison to those treated with lower dose chemotherapy.[26] Patients receiving larger doses of chemotherapy had significantly greater MCV values and lower mean platelet counts for the entire length of the 40-month observation period. A study involving 1,939 Hodgkin disease survivors highlights a similar correlation between decreased platelet counts in the course of the follow-up period and an increased risk for t-AML.[27]

Injury to hematopoietic stem cells is thought to be in part caused by telomere shortening as a consequence of chemotherapy, with repeated cycles of hematopoietic regeneration.[28] Occult bone marrow dysfunction may occur in the face of a normal complete blood count. For instance, in a study involving six children who developed t-AML after treatment for neuroblastoma, the diagnosis was found incidentally in routine bone marrow testing in four of the patients.[29] Other studies also describe *in vitro* evidence of treatment-induced bone marrow damage in asymptomatic patients.[30-32]

There were no cases of t-AML or t-MDS in this cohort, although this study did exclude at least one patient with t-AML who died less than five years from diagnosis. In long-term follow-up of childhood cancer survivors, blood count abnormalities were a common finding. Whether or not this is indicative of clinically significant marrow dysfunction that will worsen with time is not known. Further it is not known if this population with previous myelotoxic therapy will face an increased risk of MDS or other marrow abnormalities, such as anemia of chronic disease, as they enter their later decades of life. There was only a slight decrease in the frequency of abnormal MCVs and hemoglobin values over time. Therefore, it is possible that bone marrow damage after cancer treatment is permanent.

In this study, increasing epipodophyllotoxin doses were found to correlate with increased likelihood of obtaining high MCV values. For each dose range increase in epipodophyllotoxin, there was a 60% increase in the likelihood of having an abnormally high MCV value. Black race was associated with lower hemoglobin levels, likely due in part to the increased incidence of thalassemia trait in this group of

patients, and also with increased frequency of low WBC count. Both of these findings are consistent with known ethnic differences in hemoglobin concentrations and WBC counts in the normal population.[33,34] Interestingly, patients who received radiation therapy were less likely to have low hemoglobin concentrations and low platelet counts. This association may reflect less intensive chemotherapy in these patients.

Markedly abnormal CBC values were infrequent as summarized in table 4. Generally, an underlying condition was present which could explain the abnormal blood count measure. For example, iron deficiency anemia was a common finding among patients with markedly low hemoglobin concentrations.

There are several limitations of this study. First, this was a retrospective chart review with a relatively small sample size. Second, the cohort was biased by selection of those individuals who are followed in the ACE program, possibly resulting in an over estimate of the frequency of abnormalities. Finally, potential co-morbid conditions such as infection or anemia due to unrelated causes could have confounded the findings.

In conclusion, mildly abnormal CBCs are common in childhood cancer survivors. Marked abnormalities were infrequent and were generally explained by an underlying condition. Abnormalities of the four CBC components measured seemed to persist over a prolonged portion of the follow-up period. Generally, abnormal CBCs obtained during long-term follow-up are not clinically significant, and do not appear to reflect preleukemic changes. This study provides evidence for the common observation of abnormal blood counts during long-term screening and may contribute to the optimization of follow-up guidelines.

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VITAE

Zsofia Banhegyi Long was born in Cered, Hungary on August 16, 1978 as the third daughter to Zsuzsanna and Zsolt Banhegyi. She spent her 11th grade in the United States as an exchange student. After graduating from Karinthy Frigyes high school in Budapest, Zsofia entered the Honors College of Louisiana State University, in Baton Rouge, Louisiana. She majored in Biochemistry and Zoology. As part of the requirements for graduation from the Honors College, she conducted research under the supervision of Sue G. Bartlett, PhD in the Department of Biochemistry at Louisiana State University. Her goal was to learn about the full open reading frame and spatial pattern of expression of beta carbonic anhydrase in *Arabidopsis thaliana*. Her work culminated in the completion of an Honors Thesis. Zsofia graduated Summa Cum Laude from Louisiana State University, in addition she received the University Medal for graduating with a perfect 4.0 grade point average. She married Palmer R. Long III in June, 2000. Zsofia entered medical school at the University of Texas Southwestern Medical Center in 2001. She decided to explore the path of clinical research, and she started a project with the mentorship of Kevin C. Oeffinger, MD. Zsofia spent her summer months and additional time during the rest of her medical school investigating complete blood counts of childhood cancer survivors. She will earn Doctor of Medicine, with Distinction in Research in June, 2005. Zsofia plans to become a pediatrician.

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