

A Comparative Study of the Long Term Psychosocial Functioning of Childhood Acute Lymphoblastic Leukemia Survivors Treated by Intrathecal Methotrexate with or without Cranial Radiation

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BACKGROUND. Although previous research has delineated medical, cognitive, and neuropsychologic late effects of central nervous system (CNS) prophylaxis for childhood acute lymphoblastic leukemia (ALL), it has been difficult to draw conclusions about the long term psychosocial sequelae of these treatments due to methodologic problems that led to inconclusive results in past studies. In the current study, the authors examined the long term psychosocial functioning of childhood ALL survivors who had been treated on a Phase III clinical protocol (Cancer and Leukemia Group B [CALGB] 7611) between 1976 and 1979, in which they were randomized to receive either 2400 centigray of cranial radiation (CRT) with intrathecal methotrexate (IT-MTX) or intermediate dose systemic methotrexate (IV-MTX) with IT-MTX.

METHODS. One hundred ten survivors of childhood ALL (mean age, 20.8 years) treated on CALGB 7611 who were age 14 years or older and disease free for at least 1 year were studied a mean of 14.7 years after their entry on CALGB 7611. In a telephone interview, a psychosocial assessment battery was administered to the patients, consisting of measures that assessed psychologic, sexual, social, and vocational functioning as well as any delayed physical effects.

RESULTS. Survivors who had received CRT + IT-MTX had significantly poorer academic achievement ($P = 0.0001$), poorer self-images with regard to their bodies ($P = 0.001$), and greater psychologic distress ($P = 0.005$).

CONCLUSIONS. Cranial radiation used to treat children with ALL has significant long term sequelae in terms of poorer academic achievement and psychosocial functioning. These data add weight to the conclusion that CRT prophylaxis should only be used to treat children who are at high risk of CNS relapse. *Cancer* 1998;82:208-18. © 1998 American Cancer Society.

KEYWORDS: childhood cancer, cancer survivors, acute lymphoblastic leukemia, psychosocial functioning, medical oncology, radiation therapy.

Treatments have dramatically increased the 5-year survival rate in childhood acute lymphoblastic leukemia (ALL) from 4% to 73%.¹

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There has been much interest in the delayed effects that this increasingly larger cohort has experienced in terms of physical, psychologic, social, neurologic, and neuropsychologic sequelae. Late effects of childhood ALL that have been identified are an increased incidence of second malignancies (20 times expected),² organ defects,³ growth retardation,^{4,5} sterility,⁶ and cognitive and neuropsychologic deficits.⁷⁻¹⁴ Studies assessing the cognitive and neuropsychologic sequelae in children who received central nervous system (CNS) prophylactic treatment involving cranial irradiation (CRT) and intrathecal methotrexate (IT-MTX) have reported lowered intelligence and school achievement,^{11,12} lowered motor skills and sensory perceptual abilities,² and altered nondominant hemispheric functioning.¹³ It has been suggested that CRT causes more severe neuropsychologic sequelae than IT-MTX.^{13,14}

Despite the sequelae outlined above, conclusions regarding the effects of CNS prophylaxis on psychosocial functioning have been difficult to achieve. Some studies have demonstrated that ALL and other childhood cancer survivors have normal school, job, and marital status as well as normal emotional development.^{3,15-19} However, a series of adaptation problems have been identified among a subset of survivors of childhood cancer. Twenty-one percent of childhood cancer survivors were found to have moderate-to-severe psychologic problems as well as significantly lowered self-esteem.²⁰ Approximately one-fourth of adolescent survivors of childhood cancer were preoccupied with their physical condition and had problems with self-image regarding their bodies,¹⁵ and these preoccupations were noted to increase the older the adolescent was at the time of diagnosis.²¹ Depression was also found to increase with age at the time of diagnosis in pediatric cancer survivors.²² Longer course of treatment, relapse, a nonsupportive family, and disease onset at a later age have each been associated with problems in long term adjustment for survivors of childhood cancer.²³ Re-entry problems and difficulty obtaining health and life insurance have been reported for both childhood and adult survivors.^{17,18,24} Studies of school re-entry have found that the amount of time spent in medical settings reduced school attendance and performance²⁵ and that the effects of treatment on body image resulted in decreased self-esteem, which subsequently lowered school performance.²⁶ ALL survivors were also found to be more likely than sibling controls to enter special education and less likely to be placed in programs for gifted students.²⁷ In this study, higher doses of radiation were associated with increased need for special education interventions and decreased enrollment in college. In-

terpretation of some of these findings concerning survivors' adjustment has been complicated by study design issues that have led to difficulty in comparing findings among studies. Varying sample sizes, diagnoses, inclusion criteria, treatment differences, relapse status, time from treatment to study, and choice of instruments assessing psychosocial functioning have contributed to the ambiguity of findings and difficulty in arriving at firm conclusions about the long term functioning of children treated by CNS prophylaxis for cancer.

An understanding of the long term psychosocial effects of various forms of CNS prophylaxis is important in making determinations regarding the form of treatment used. Although CRT has been implicated as having more severe neuropsychologic and school performance effects, more definitive findings comparing the specific psychosocial effects of the two most common forms of CNS prophylaxis, CRT and IT-MTX, are limited. The current study examined the long term psychosocial functioning of children with ALL randomized to receive IT-MTX with or without CRT. These children were treated between 1976 and 1979 in a multicenter Phase III clinical protocol (Cancer and Leukemia Group B [CALGB] 7611), in which they were randomized to receive either 2400 cGy CRT + IT-MTX or intermediate dose systemic methotrexate (IV-MTX) + IT-MTX. Recent follow-up of these children at 12 years revealed almost identical survival across the two treatment arms. However, significantly better bone marrow ($P = 0.0005$) and testicular protection ($P = 0.004$) was provided for those in the IV-MTX + IT-MTX arm, and better CNS protection was provided for those in the CRT + IT-MTX arm ($P < 0.0001$).²⁸ The similar survival data for the two groups made it particularly compelling to examine the overall level of long term psychosocial functioning of this cohort in whom medical and treatment variables were controlled. Given the relative severity of the neuropsychologic sequelae associated with CRT versus IT-MTX¹⁰ and the increase in education problems associated with higher doses (2400 cGy) of radiation,²⁷ it was predicted that survivors from the CRT + IT-MTX arm would have worse adaptation than those from the IV-MTX + IT-MTX group.

METHODS

Patients

Survivors enrolled in this study had been randomized to treatment for ALL on the protocol CALGB-7611, were at least age 14 years at the time of the study, had been free of disease for at least 1 year, were English-speaking (with the exception of one institution for which the survey was translated), and were treated at

an institution that agreed to participate in this long term follow up study. In 1991, 320 children were alive as of the last date of contact.²⁸ One hundred eighteen were excluded for the above reasons, resulting in 202 children who were eligible for the survey. One hundred seventeen (60%) were located and 110 (94%) of these patients agreed to participate in the study. To address generalizability, the patients who agreed to participate were compared with the 92 who could not be located or chose not to consent in terms of randomized treatment, gender, race, age at the time of the study, and number of relapses. The two groups did not differ statistically regarding any of these characteristics, with all *P* values greater than 0.22. There was a significant difference, however, in age at the time of treatment. Those interviewed were significantly older at the time of treatment (mean age, 6.5 years) than those not interviewed (mean age, 4.6 years) ($P < 0.01$).

Procedure

Patients received an appointment for a telephone interview 10–14 days after their agreement to participate. They received the consent form and a copy of the Psychosocial Assessment Battery by mail and were asked to return the consent form in a stamped, self-addressed envelope. For patients younger than 18 years, consent forms were also mailed to the parents. Patients were instructed to complete the battery prior to the telephone interview. The 60- to 90-minute telephone interview was carried out by a trained research interviewer and clinical psychologist (J.M.H.), who asked the patient's response to each question and recorded it. Using only one trained interviewer controlled for reliability. Clarification of questions was given as needed. The telephone interview method and the core assessment instruments used have also been used in other CALGB studies of adult leukemia and Hodgkin's disease survivors.²⁹

Measures

The Psychosocial Assessment Battery consisted of measures that assessed the patient's psychologic, sexual, social, and vocational functioning. Physical functioning and the presence of any delayed effects commonly associated with cognitive impairment and growth retardation were queried. In addition, several factors that modulated the level of psychosocial adaptation were also assessed: sociodemographic characteristics, family environment, and health beliefs. The battery was modified for adolescents with the addition of the Achenbach Child Behavior Checklist³⁰ and deletions of items from the adult battery of measures (Body Image Scale, Sexual Problem Index, Domestic Envi-

ronment, and Sexual Relationships subscales of the PAIS) that were inappropriate for this age group.

Psychosocial Adjustment to Illness Scale (PAIS) (Self-Report)

Developed by Derogatis,³¹ the PAIS is a 45-item inventory of 7 dimensions of adjustment to illness: health beliefs; patient satisfaction; vocational, domestic, and social environment; sexual relationships; extended family relationships; and psychologic distress. Each item has four-point response categories that reflect increasing degrees of maladjustment. The Domestic Environment and Sexual Relationships subscales were deleted from the Adolescent Battery. A PAIS "amended" total score reflected only those subscales administered to both adults and adolescents.

Brief Symptom Inventory (BSI)

A brief version of the 90-item Symptom Checklist (SCL-90), the BSI³² consists of 53 symptoms grouped into the following 9 subscales: somatization, obsessive-compulsive disorder, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Each symptom was rated on a 5-point scale of frequency over previous 2 weeks, from 0 (not at all) to 4 (extremely). The Global Severity Index is expressed as a mean, ranging from 0 to 4.

Impact of Event Scale

The Impact of Event Scale³³ is a 15-item scale measuring 2 dimensions of response to traumatic events (in this case, having leukemia): intrusive thoughts about the trauma, or attempting to block or avoid reminders of the event. Each item is rated on a 4-point weighted scale of frequency, ranging from 0 to 5, with the total score ranging from 0 to 75.

Conditioned Nausea and Vomiting Index

This scale, developed by Cella et al.,³⁴ consists of six items asking whether any sights, smells, or tastes were reminders of treatment that triggered nausea, vomiting, or psychologic distress within the past year. Each item is rated on a 10-point reaction scale, with greater scores indicating more severe reactions, and the total Conditioned Nausea and Vomiting Index ranging from 0 to 60.

Sexual Problem Index (Adult Battery only)

In addition to the sexual relationships subscale of the PAIS,³¹ the following areas of sexual functioning were assessed: interest, activity, sense of attractiveness, acceptance by a partner, and interest in having a child. Regarding each problem, the survivor was queried as

to whether he or she attributed it to having had leukemia.

Body Image Subscale

The Body Image Subscale of the Sexual Functioning Inventory³⁵ was used to assess the impact of having had childhood ALL on sexual body image. These items were rated on a 4-point scale, with higher scores indicating worse body image.

Employment and Insurance Difficulties

Survivors were asked whether any of a list of 21 possible negative occurrences involving employment and insurance had happened to them (e.g., being denied a promotion or health coverage) and whether these experiences could be attributed to having had leukemia. The number of problems attributed to having had cancer formed the Employment Index and Insurance Index.

Family Functioning Scale

Family functioning was assessed as a predictor of adaptation with a scale developed by one of the authors (A.B.K.) based on the literature^{36–40} and previously used in CALGB protocols. The Family Functioning Scale consists of 30 items, each rated on a 5-point Likert scale, with 5 subscales: family cohesion, adaptability, support, conflict, and communication. The scale's reliability is excellent, with an alpha coefficient of 0.94.

Multidimensional Health Locus of Control (MHLC)

The MHLC Scale⁴¹ is an 18-item scale designed to assess 3 dimensions of perceived control over one's life: internal control, chance, and powerful others. Items are rated on a 5-point Likert scale ranging from "strongly agree" to "strongly disagree," with the subscale total scores ranging from 6 to 30.

Fear of Relapse

Five items, created by one of the authors (A.B.K.), assess a patient's beliefs and anxieties about a possible relapse of leukemia. Each item is rated on a 5-point Likert scale, from "strongly agree" to "strongly disagree." The score ranges from 5 to 25, with a higher score reflecting a greater fear of relapse. Reliability is acceptable, with an alpha coefficient of 0.69.

Delayed Medical Effects

Specific questions were asked about any physical symptoms that might reflect delayed CNS prophylaxis effects: visual problems, fine motor skills, and menstrual problems. Each subject was asked for their height and a measure of their head size. Subjects who

did not know their head size were instructed on how to measure its circumference. These measurements were then compared with age specific developmental norms to determine whether the survivor presented with either abnormal height or abnormal head size.

School Achievement and Socioeconomic Resources

Information concerning current education, school achievement, employment status, occupation, income, health insurance, and marital status were obtained. Patterned after the Achenbach Child Behavior Checklist (see description below), school achievement for all survivors was assessed by calculating the overall average of survivors' ratings of their most recent performance in English, history, social studies, arithmetic, and science on a 4-point scale, from "failing" to "above average." Survivors' perceptions of any negative socioeconomic impact of their illness was assessed by determining their current socioeconomic status and how they thought it might have been impacted by leukemia. A Perceived Negative Socioeconomic Impact Index was created from this information, based on survivors' currently having a lower status from 1 year before diagnosis regarding family income and education as compared with what they thought they would have had if they had not developed leukemia. With a score of 0–1 for each status, the total score for the Perceived Negative Socioeconomic Impact Index ranges from 0 to 2.

Achenbach Child Behavior Checklist: Youth Self-Report Form (Adolescent Battery only)

The youth self-report form of the Achenbach Child Behavior Checklist³⁰ for ages 11–18 years was administered to survivors ages 14–18 years. It consists of 119 questions classified into subscales of activities, social functioning, school performance, and behavioral problems.

Statistical Methods

Treatment arm differences in demographic and medical variables involving categorical data were examined using the chi-square test unless otherwise specified. To examine the differential long term impact of the two prophylactic CNS therapies on the psychosocial adaptation of survivors of childhood ALL, two-way multivariate analysis of covariance (MANCOVA) was used, with the treatment arms (CRT + IT-MTX vs. IV-MTX + IT-MTX) as the independent variables and the age of entry into treatment as the covariate. The dependent variables included in this analysis were the PAIS amended total, Body Image, School Achievement, and Fear of Relapse scores. This analysis was followed by univariate testing in which two-way analy-

sis of variance was used to ascertain sources of significance. A separate 2×2 MANCOVA, with treatment arm and age group (adolescent vs. adult) entered as the independent variables, was performed to assess the effect of age at interview on survivors' adaptation. A logarithmic transformation of the Body Image Subscale and a Box and Cox power transformation⁴² of School Achievement (adults) were performed to meet MANCOVA's statistical assumptions of normality. The transformed variables are indicated in Tables 2 and 3. Due to multiple comparisons, the Bonferroni adjustment to the alpha level was applied.

Initially, other dependent variables were considered for analyses in which MANCOVA was used; but because assumptions involving normality were violated, they were not included in these analyses. Treatment arm differences involving the PAIS subscales were therefore tested using Wilcoxon's rank sum test. The BSI Global Severity Index score was divided into three categories to reflect levels of severity of psychological distress: low to no evidence of distress (<0.5 standard deviation [s.d.] above the normative mean), moderate distress (0.5–1.49 s.d. above the normative mean), and high distress (1.5 s.d. or greater above the normative mean). This division of scores was based on Derogatis's³¹ recommendation that scores of 1.5 s.d. above the mean of the BSI be used as a benchmark for a possible psychiatric disorder that would require further evaluation. Logistic regression analyses⁴³ were used to identify factors that were predictive of school achievement and psychological distress as defined by these BSI categories. Because only one survivor was classified in the high distress category, moderate and high distress groups were combined for purposes of the logistic regression. Logistic regression was also used to test the predictive value of treatment arm and age at protocol entry of conditioned nausea and vomiting, dichotomized as either present or absent due to the highly skewed data. Stepwise regression analysis was used to identify significant treatment, sociodemographic factors, and psychosocial characteristics that were predictive of Fear of Relapse.

RESULTS

Descriptive, demographic, and relevant medical variables are presented in Table 1 by treatment arm and age interviewed. Patients younger than 18 years at the time of the interview were included in the adolescent group, and those age 18 years and older were defined as adults. No significant differences between treatment arms were found in terms of gender composition, marital status, frequency of CNS relapse, bone marrow relapse, or testicular relapse.

Using MANCOVA, survivors who had received

CRT + IT-MTX had significantly worse body image ($P = 0.001$), lower school achievement ($P = 0.0001$), and a tendency towards worse overall adjustment (PAIS Amended Score $P = 0.049$, which is above the more stringent alpha needed for multiple comparisons) than those who received IV-MTX + IT-MTX (Table 2). Neither treatment arm nor age at protocol entry were found to be significant predictors of conditioned nausea and vomiting when tested using logistic regression analysis.

To examine the effect of age at interview on survivors' adaptation, a separate 2×2 MANCOVA was performed, with treatment arm and age group (adolescent vs. adult) entered as the independent variables; the PAIS Amended Score, Body Image, School Achievement, and Fear of Relapse as the dependent variables; and age at clinical entry as the covariate. The combined dependent variables were affected to a highly significant degree by both treatment arm ($P = 0.0001$) and age group at interview ($P = 0.0001$), with the significance level of the interaction of the two ($P = 0.026$) slightly above the Bonferroni adjustment of the alpha level. When the dependent variables were independently examined (Table 3), there was a trend for adolescents in the IV-MTX + IT-MTX to have better adjustment with lower PAIS amended scores ($\bar{X} = 2.8$, s.d. = 1.3) than all other groups (adult IV-MTX + IT-MTX: $\bar{X} = 7.7$, s.d. = 0.66; adolescent CRT + IT-MTX: $\bar{X} = 8.3$, s.d. = 1.1; adult CRT + IT-MTX: $\bar{X} = 8.7$, s.d. = 0.85). However, with the Bonferroni adjustment of the alpha level to $P = 0.0125$, statistical significance was not met.

As not all PAIS subscales had been appropriate for adolescent survivors, MANCOVAs were separately performed for the adolescents and adults at the time of the interviews to test for treatment arm differences on specific PAIS subscales. For adults, there were no significant differences between treatment arms on any of the PAIS subscales, as determined by Wilcoxon's rank sums test. For adolescents, those in the CRT + IT-MTX group were more likely to have significantly worse vocational/school functioning (PAIS Vocational Environment) than those in the IV-MTX + IT-MTX arm ($P = 0.003$, Wilcoxon's rank sum test).

Stepwise logistic regression analyses were performed using the dichotomized BSI Global Severity categories as the dependent variable (90% low-to-no distress vs. 10% moderate-to-high distress), and the following variables as predictors: age at the time of protocol entry, gender, treatment arm, relapse status, length of time since treatment completion, abnormal height, abnormal hat size, subsequent illness or complications since treatment completion, Locus of Control subscale scores, and School Achievement. Treat-

TABLE 1
Sociodemographic Data and Medical Characteristics

	CRT + IT-MTX		Intermediate dose MTX + IT-MTX	
	Adolescents	Adults	Adolescents	Adults
n = 110	19	33	13	45
Gender				
Female	42.1%	36.4%	38.5%	53.3%
Male	57.9%	63.6%	61.5%	46.7%
Age (Mean, yrs)	16.7	23.8	16.6	21.6
Age at dx. (Mean, yrs)	2.7	9.2	2.6	7.1
Time from dx. to interview (Mean, yrs)	14.4	14.9	14.6	14.7
Race				
White	90%	89%	91%	88%
Black	6%	5%	4%	7%
Asian	4%	6%	5%	4%
Other	0%	0%	0%	1%
% Relapsed	42.1%	27.3%	30.6%	22.2%
% CNS relapse	15.8%	9.1%	15.4%	17.8%
% BM relapse	26.3%	6.1%	15.4%	6.7%
% Testicular relapse	5.3%	12.1%	0%	2.2%
% with abnormal height	10.5%	0%	0%	6.7%
% with abnormal head size	63.2%	63.6%	53.9%	42.2%
Marital status				
Married	—	45.5%	—	24.4%
Single	—	51.5%	—	71.1%
Divorced	—	3.0%	—	4.4%
Income				
\$5,000–14,999	—	33.3%	—	28.9%
15,000–29,999	—	27.3%	—	22.2%
30,000–44,999	—	36.4%	—	42.2%
45,000+	—	3.0%	—	6.7%

CRT: cranial radiation; IT: intrathecal; MTX: methotrexate; dx.: diagnosis.

TABLE 2
Comparison of Cranial Radiation with Intermediate Dose MTX for Total Sample (MANCOVA)^a

		CRT + IT-MTX (n = 52)	Intermediate dose MTX + IT-MTX (n = 58)	
PAIS amended total	\bar{X}	8.6	6.7	$P = 0.049$
	sd	(5.1)	(4.1)	
Body image ^b	\bar{X}	10.1	7.9	$P = 0.001$
	sd	(0.47)	(0.45)	
School achievement ^c	\bar{X}	1.7	2.2	$P = 0.0001$
	sd	(0.07)	(0.06)	
Fear of relapse ^d	\bar{X}	9.7	9.1	$P = 0.27$
	sd	(2.9)	(2.4)	

MANCOVA: two-way multivariate analysis of covariance; CRT: cranial radiation; IT: intrathecal; MTX: methotrexate; PAIS: Psychosocial Adjustment to Illness Scale.

^a Covariate = age of entry on Cancer and Leukemia Group B 7611; adjusted mean presented.

^b High score indicates worse adjustment (PAIS) and worse body image.

^c High score indicates greater achievement.

^d High score indicates greater fear of relapsing.

ment Arm ($P = 0.025$), Internal Locus of Control ($P = 0.005$), School Achievement ($P = 0.034$), and Powerful Other subscale ($P = 0.049$) were significant predictors of BSI Global Severity categories. Patients who received CRT were 15.8 times more likely to have moderate-to-high distress (95% confidence interval [CI], 1.4–175.4). In addition, for every unit decrease in School Achievement, the risk of moderate-to-high distress increased 2.56 times (95% CI, 1.7–3.9); for every unit increase in Internal Locus score, the risk of moderate-to-high distress increased 1.5 times (95% CI, 1.1–2.1); and finally, for every unit decrease in the Powerful Other score, the risk of moderate-to-high distress increased 0.7 times (95% CI, 0.50–0.99). To test for the effect of mediating factors on distress, a second logistic regression was calculated, with interaction terms entered, including treatment arm by Internal Locus score, School Achievement, and Powerful Other subscales, along with the other predictors listed above. None of the interaction terms were significant.

Regression analyses were also performed to deter-

TABLE 3
Comparison of Psychosocial Adaptation by Treatment Arm and Age Group (MANCOVA)

Dependent variable	CRT + IT-MTX n = 52 X̄ (sd)	IV-MTX + IT-MTX n = 58 X̄ (sd)	P value	Adoles. n = 32 X̄ (sd)	Adult n = 78 X̄ (sd)	P value	Interaction P value
PAIS amended total	8.5 (.64)	5.2 (.72)	0.0009	5.5 (.93)	8.2 (.55)	0.026	0.018
Transformed body image ^a	2.3 (.05)	2.1 (.06)	0.054	2.4 (.08)	2.0 (.05)	0.0001	0.41
Transformed school achievement ^b	3.1 (.26)	4.8 (.29)	0.0001	3.4 (.38)	4.5 (.22)	0.015	0.25
Fear of relapse	9.7 (.38)	9.1 (.43)	0.27	9.3 (.56)	9.4 (.33)	0.91	0.92

MANCOVA: two-way multivariate analysis of covariance; CRT: cranial radiation; IT: intrathecal; IV: intravenous (intermediate dose); MTX: methotrexate; PAIS: Psychosocial Adjustment to Illness Scale.

^a Log of body image is used in the model.

^b Square of school achievement is used in the model.

mine the combination of factors that significantly predicted the Fear of Relapse score. The more survivors perceived their illness to be controlled by chance, the less they feared relapse ($P = 0.0001$). When the regression analysis included the Family Functioning Scale, thus restricting the analysis to the subset of survivors who were living with one or more family members ($n = 81$), greater fear of relapse was significantly related to the less they perceived their health to be controlled by chance ($P = 0.0001$) and worse school achievement ($P = 0.047$).

A fourth regression analysis was performed with the School Achievement scale as the dependent measure and predictors including: gender; age at the time of protocol entry; treatment arm; relapse status; years since treatment completion; and subsequent illnesses. Significant predictors of poorer school achievement were CRT + IT-MTX ($P = 0.0001$) and younger age at diagnosis ($P = 0.014$), which both accounted for 20% of the school achievement variance ($P = 0.0001$, $r^2 = 0.20$).

A final logistic regression analysis was performed to test the predictive value of family functioning on distress, using 81 of the 110 survivors who were living with one or more family members. The Family Functioning total score was the single best predictor of distress level ($P = 0.002$), with poorer family functioning predictive of greater distress.

In terms of delayed physical effects, there was a significantly greater proportion of survivors who had CRT + IT-MTX with abnormal head sizes than those who had IV-MTX + IT-MTX (chi-square test, $P = 0.05$). These treatment differences in head size were examined by age group, with a tendency for significant differences in the adolescent group only (chi-square test,

$P = 0.06$). No significant differences were found between groups in incidence of abnormal height.

DISCUSSION

The results of this study consistently demonstrated the long term negative consequences of CRT for psychosocial adjustment and academic achievement in survivors of childhood ALL who had been treated approximately 15 years previously. These long term effects of significantly worse school achievement and greater psychologic distress for those receiving CRT + IT-MTX than those receiving IV-MTX + IT-MTX held even when the data were separately analyzed by adolescent and adult subgroups. Because survivors were randomly assigned to treatment arms, alternative explanations for these findings due to confounding factors of disease, treatment, and sociodemographic characteristics were unlikely.

School Achievement and Psychologic Adjustment

Prophylactic CRT, either alone or in combination with intrathecal chemotherapy, has been associated with long term neuropsychologic effects on intelligence and academic achievement^{7-14,27} in survivors of childhood cancer, with the effects more pronounced when children younger than 4-6 years are treated.⁴⁴ Our results are not only consistent with these findings but also suggest the importance of school achievement to survivors' subsequent psychologic state and vocational adjustment. In addition to CRT + IT-MTX, lower school achievement was found to be a significant predictor of greater psychologic distress and was significantly correlated with current vocational functioning in young adults ($r = 0.27$, $P < 0.02$). Time missed from school due to treatment and the psychologic trauma of

being treated for cancer^{25,45} may have also significantly affected school achievement, in addition to the neurotoxic effects of CRT. As it was not possible to assess time missed from school or baseline psychologic status, we were not able to determine the influence of these variables on school achievement.

Despite the significant effects of CRT on school achievement and the higher levels of distress in these individuals, only one person reported a significantly high level of psychologic distress, and 9% reported moderate distress. A small subset of young adult survivors (8%) perceived that having been treated for cancer resulted in a negative impact on their employment status. Only 13% reported conditioned nausea and distress in response to treatment-related stimuli. Research has generally concluded that there is a normal level of psychologic adjustment among childhood cancer survivors.⁴⁶ In several studies, no differences have been found in adjustment between cancer survivors and healthy controls in terms of psychologic or sexual adjustment, body image, education, employment, occupational status, vocational adjustment, or marital status.^{46,47} In fact, survivors have demonstrated psychosocial advantages in a number of studies: a greater sense of well-being among adult survivors of childhood cancer than among their peers, and perceptions of greater empathy, maturity, and goal direction as a result of their experience.¹⁵ Thus, it would appear that for many patients, with time and maturation, there is an ability to compensate for the neuropsychologic deficits and reduced academic performance that are consequences of prophylactic CRT. However, when our results are viewed in their totality, there is clear evidence of nonpathologic but subclinical “enduring psychological consequences”¹⁵ (p.713) of being treated for childhood cancer.^{20,46}

Family Functioning and Beliefs of Control over Health as Predictors of Psychologic Distress

A worse family environment significantly predicted greater psychologic distress in survivors, in addition to CRT and poor school achievement. Having supportive families has correlated with better adjustment in several studies of childhood cancer survivors.^{20,48} In these studies as well as ours, family functioning and psychologic state were both based on patients’ reports of their current status, making causal interpretations difficult. It is clear that the cancer survivor and his/her family are in an interactive relationship, mutually influencing each other. However, in keeping with much of the social support literature,^{49,50} the effect of the family environment likely impacts on the survivor’s psychologic state rather than the reverse. It will only be through longitudinal assessment elucidated

by path analysis, and experimental interventions designed to improve either family functioning or a survivor’s psychologic state, that the causal sequence between these two entities will begin to be disentangled.⁵¹ Our data clearly indicate that the leukemia survivors who were less distressed were more likely to report that their family environment was supportive and more cohesive and had less conflict.

A recurrent theme among survivors of cancer is feeling a loss of control over their lives as a consequence of the disease.^{23,52,53} Serious illness imposes restrictions on a child’s daily activities, results in greater dependency on others, and threatens short and long term goals as well as the patient’s very life. The survivorship experience can partly be characterized as a regaining of control over one’s life, which for a prolonged period of time was lost. Learned helplessness has been proposed⁵² as the theoretical model to explain the relationship between cancer patients’ perceptions of control over traumatic illness and depression, underscoring the viewed importance of personal control over health to subsequent adjustment. It was therefore not surprising when our data demonstrated that survivors’ psychologic states were significantly influenced by their perceptions of control over their health. Those who did psychologically better were those who felt less personal responsibility regarding their illness. Having cancer controlled by their doctors (i.e., “powerful others”) and/or by chance or fate was preferable to feeling that they were personally in control. These findings are contrary to one study demonstrating better adjustment in childhood cancer patients with a greater sense of personal control.⁵³ Rather, the data from our study are suggestive of the conclusion drawn by Reid,⁵⁴ that for cancer survivors, living with a chronic disease or the threat of recurrence “fosters the development of externality in one’s attitudes. Indeed, becoming more external seems to be an adjustive strategy...” (p.365). Although some health-related matters are within patients’ control, such as health screening behaviors and following treatment recommendations, there is much about the disease process that is not under their control. Our findings indicate that better adjustment requires survivors to come to terms with this distinction.

Issues Specific to Young Adult Survivors

The 2 × 2 MANCOVA and the separate analyses of young adults and adolescents revealed that there were several issues specific to adults, some of which were age-appropriate developmental concerns. Young adults who had received CRT + IT-MTX reported significantly worse body image. This factor, in addition to worse school achievement and greater psychologic distress, indicated

a broad-based constellation of problems in adult adjustment that generally did not appear to reach pathologic levels, stemming from having been treated with CRT + IT-MTX.

Differences in body image between treatment groups were expected, in light of previous research demonstrating endocranial abnormalities resulting in growth retardation for those who had received prophylactic CRT^{5,6} and studies demonstrating growth retardation in children exposed to A-bomb radiation in Hiroshima and Nagasaki.⁵⁵⁻⁵⁷ The significantly smaller head sizes of those who received CRT + IT-MTX may have in part contributed to poorer body image among young adult survivors. However, it is possible that other factors also played a role. Negative body image has been reported in adolescent cancer survivors with mixed diagnoses^{15,47} as well as survivors of adult onset acute leukemia.⁵⁸ On finding no differences in body image between adult acute leukemia survivors who had received bone marrow transplant vs. conventional chemotherapy, Mumma et al.⁵⁸ suggested that having been treated for cancer may have been related to poorer body image in the group as a whole—the perception that their bodies “have to some extent failed them” (Cella,⁵⁹ p.150). This may have been particularly keenly felt by our young adult survivors who had received prophylactic CRT + IT-MTX at the time they were in school, struggling to keep up academically while experiencing alopecia and competing with healthy peers. The adjustment of childhood cancer survivors whose illness occurred at a very early age has been associated with better outcome than when illness occurred at an older age.²⁰ Our young adult survivors may be cases in point.

Limitations of the Study

Although clear differences across the two treatment arms were demonstrated in this study, elements of the design limited the conclusions that could be drawn from the data. Interpretations regarding the clinical significance of the achievement findings were limited by the subjective nature of the self-reports utilized and possibly by the effects of memory on recollections of past school performance. Although objective archival school data would have strengthened the findings, gaining access to such data was outside the scope of this study.

Clinical Implications

It is clear that cancer survivors who had received CRT + IT-MTX, who as a group had demonstrably greater and more enduring difficulties in adjustment than those who had received IV-MTX + IT-MTX approximately 15 years after treatment completion, might

have benefitted from neuropsychologic and psychologic interventions soon after completing treatment. To improve academic performance, neuropsychologic rehabilitation should be considered.⁶⁰ A number of interventions have been proposed to improve children's academic performance and psychosocial adjustment on their return to the classroom. Greater use of individualized instruction and tutoring, combined with active parental support,⁶¹ could be more assiduously applied earlier to help compensate for learning deficits. Social skills training, in conjunction with the School Reintegration Program,^{62,63} is a comprehensive program to improve adjustment of children newly diagnosed with cancer on their return to school after treatment. This social skills training program is designed to help children with cancer-related interpersonal difficulties by providing supportive counseling for the child and parent, making educational presentations to school personnel and classmates concerning cancer, and establishing a hospital-based liaison between the child's oncology team and the school. Initial results indicate that this might be a valuable approach to diminishing psychosocial sequelae and improving school performance among children receiving CRT. A behavioral management program for parents, designed to improve children's school attendance and facilitate their reintegration into the classroom, is currently being tested.⁶⁴

The long term psychosocial difficulties experienced by ALL survivors need to be viewed in conjunction with the results from the clinical trial CALGB 7611, which demonstrated no survival advantage for either form of CNS prophylaxis.²⁸ Thus, in light of no demonstrated survival advantage of prophylactic CRT, coupled with this growing body of data concerning the medical and psychosocial late effects of the treatment 15 years after completion, we conclude that the continued prophylactic use of CRT to eradicate subclinical CNS involvement requires increasing justification and should only be used to treat children who are at high risk of CNS relapse. New methods of prophylactic CRT that may be more effective and less toxic than conventional CRT clearly need to be identified.⁶⁵

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