



ON-LINE FIGURE. Consort note: 369 survivors were treated according to the Total Therapy XV protocol and underwent on-therapy MR imaging. Survivors were excluded from follow-up analyses if they had relapsed and were treated with cranial radiation therapy (CRT) or bone marrow transplantation (BMT), had a second malignant neoplasm (SMN) requiring additional treatment, had a neurodevelopmental disorder (eg, prematurity with intraventricular hemorrhage), had a genetic disorder associated with neurocognitive impairment (eg, Down Syndrome), had an unrelated brain injury (eg, traumatic brain injury), or were nonfluent in English. Recruitment was not attempted for survivors who were discharged from pediatric follow-up care (ie, older than 18 years of age and >10 years from diagnosis), were in foster care, or were in prison. Finally, 295 survivors were approached and 189 (64%) of them agreed to participate in this follow-up study. Some survivors actively refused testing or brain imaging, and imaging was not attempted in those survivors who had metallic objects in their body (eg, braces). A total of 173 eligible survivors successfully underwent follow-up MR imaging of the brain. Technical (program malfunction) or behavioral (participant movement during task performance) artifacts prevented analysis of quantitative imaging data in a small subset of survivors.

On-line Table 1: Demographics and treatment characteristics by occurrence of leukoencephalopathy^a

	Persistent Leukoencephalopathy (n = 41)			No Evidence of Leukoencephalopathy (n = 121)			P ^b
	No. (%)	Mean (SD)	Median (IQR)	No. (%)	Mean (SD)	Median (IQR)	
Demographics							
Sex							
Male	22 (54)			60 (49)			.65
Female	19 (46)			61 (51)			
Race/ethnicity							
White	27 (66)			87 (72)			.37
Asian	2 (5)			1 (1)			
Black	5 (12)			16 (13)			
Hispanic	6 (15)			11 (9)			
Others	1 (2)			6 (5)			
Current age (yr)		15.1 (4.6)	14.3 (11.2–19.0)		14.0 (4.6)	12.8 (10.4–16.0)	.16
Patient's highest education (yr)		8.3 (4.1)	8.0 (4.0–12.0)		7.2 (3.8)	6.0 (4.0–10.0)	.18
Maternal education (yr)		13.7 (2.7)	13.0 (12.0–16.0)		13.5 (2.5)	13.0 (12.0–16.0)	.69
Paternal education (yr)		14.1 (3.4)	12.0 (12.0–16.0)		13.4 (3.0)	12.0 (12.0–16.0)	.55
Treatment characteristics							
Age at diagnosis (yr)		7.2 (4.6)	6.2 (3.4–10.8)		6.3 (4.0)	5.1 (3.5–8.3)	.51
Time since diagnosis (yr)		7.9 (2.0)	7.3 (6.3–9.3)		7.6 (1.6)	7.5 (6.3–8.9)	.65
Treatment risk stratum							
Low	23 (56)			75 (62)			.51
Standard/high	18 (44)			46 (38)			
Chemotherapy doses^c							
Oral dexamethasone (mg/m ²)		1074.7 (306.5)	1098.3 (991.5–1182.0)		1106.0 (301.1)	1099.8 (995.2–1348.9)	.67
IV high-dose cytarabine (g/m ²)		7.5 (1.3)	8.0 (8.0–8.0)		9.0 (4.2)	8.0 (8.0–8.0)	.15
IV doxorubicin (mg/m ²)		110.1 (57.8)	62.5 (60.7–179.1)		109.2 (56.4)	62.9 (60.7–177.8)	.66
IV leucovorin (mg/m ²)		338.3 (155.8)	315.0 (220.0–390.0)		346.7 (218.5)	300.0 (200.0–395.0)	.26
IV high-dose methotrexate ^d (g/m ²)		14.6 (4.6)	13.9 (10.6–18.3)		15.6 (7.0)	14.1 (11.4–19.1)	.45
IT MHA (No. of counts)		14.8 (3.6)	15.0 (12.0–16.0)		14.4 (4.2)	12.0 (12.0–16.0)	.13

Note:—IQR indicates interquartile range; IT MHA, intrathecal injection of methotrexate plus hydrocortisone plus cytarabine.

^a“Persistent leukoencephalopathy” refers to survivors who presented with leukoencephalopathy both during active therapy and follow-up. “No evidence of leukoencephalopathy” refers to survivors with no leukoencephalopathy detected during both active therapy and follow-up.

^bP compares demographic and treatment characteristics between survivors with persistent leukoencephalopathy and survivors with no evidence of leukoencephalopathy.

^c Except for IT MHA, all drug doses are presented as cumulative doses (g/m² or mg/m²).

^dHigh-dose IV methotrexate was defined as daily dose of >1 g/m² of IV methotrexate.

On-line Table 2: Association between persistent leukoencephalopathy and white matter integrity

Tracts	Mean Diffusivity (95% CI)			Fractional Anisotropy (95% CI)		
	Persistent Leukoencephalopathy (n = 39)	No History of Leukoencephalopathy (n = 117)	P ^a	Persistent Leukoencephalopathy (n = 39)	No History of Leukoencephalopathy (n = 117)	P ^a
Corpus callosum	0.925 (0.912–0.937)	0.904 (0.897–0.911)	.013 ^b	0.517 (0.506–0.529)	0.531 (0.524–0.537)	.080
Genu	0.812 (0.798–0.827)	0.791 (0.783–0.799)	.026 ^b	0.450 (0.431–0.469)	0.483 (0.472–0.494)	.013 ^b
Body	0.948 (0.932–0.964)	0.921 (0.912–0.930)	.013 ^b	0.491 (0.476–0.506)	0.513 (0.504–0.521)	.026 ^b
Splenium	0.970 (0.953–0.986)	0.952 (0.942–0.961)	.095	0.567 (0.555–0.579)	0.565 (0.559–0.572)	.81
Corticospinal tract	0.849 (0.824–0.874)	0.839 (0.825–0.854)	.75	0.451 (0.440–0.462)	0.445 (0.439–0.452)	.69
Left	0.853 (0.830–0.875)	0.838 (0.825–0.851)	.69	0.456 (0.444–0.467)	0.453 (0.446–0.460)	.82
Right	0.846 (0.816–0.875)	0.841 (0.824–0.857)	.82	0.447 (0.434–0.459)	0.437 (0.430–0.445)	.69
Medial lemniscus	0.846 (0.816–0.875)	0.841 (0.824–0.857)	.99	0.447 (0.434–0.459)	0.437 (0.430–0.445)	.99
Left	0.785 (0.768–0.801)	0.780 (0.771–0.790)	.99	0.451 (0.439–0.464)	0.453 (0.446–0.460)	.99
Right	0.777 (0.761–0.792)	0.776 (0.767–0.785)	.99	0.459 (0.446–0.471)	0.461 (0.454–0.469)	.99
Cerebellar peduncle	0.844 (0.828–0.860)	0.831 (0.822–0.840)	.59	0.446 (0.438–0.454)	0.447 (0.443–0.452)	.89
Middle	0.821 (0.802–0.841)	0.807 (0.796–0.818)	.59	0.454 (0.444–0.463)	0.457 (0.452–0.462)	.81
Pont cross tract	0.769 (0.753–0.785)	0.773 (0.764–0.782)	.87	0.369 (0.382–0.402)	0.387 (0.381–0.393)	.81
Inferior (left)	0.917 (0.894–0.939)	0.924 (0.911–0.937)	.81	0.384 (0.370–0.398)	0.383 (0.375–0.391)	.94
Inferior (right)	0.874 (0.854–0.894)	0.870 (0.858–0.881)	.87	0.372 (0.358–0.387)	0.371 (0.362–0.379)	.94
Superior (left)	1.019 (0.995–1.042)	0.997 (0.983–1.010)	.59	0.473 (0.461–0.485)	0.464 (0.457–0.471)	.59
Superior (right)	1.017 (0.994–1.040)	0.996 (0.983–1.009)	.59	0.456 (0.444–0.468)	0.452 (0.445–0.459)	.81
Cerebral peduncle	0.856 (0.841–0.871)	0.854 (0.845–0.862)	.98	0.575 (0.563–0.587)	0.577 (0.570–0.584)	.98
Left	0.858 (0.843–0.873)	0.855 (0.846–0.864)	.98	0.566 (0.554–0.578)	0.572 (0.565–0.578)	.98
Right	0.854 (0.838–0.869)	0.852 (0.843–0.861)	.98	0.585 (0.572–0.597)	0.583 (0.576–0.591)	.98
Internal capsule	0.736 (0.731–0.741)	0.733 (0.730–0.736)	.53	0.517 (0.510–0.525)	0.525 (0.521–0.529)	.42
Anterior limb (left)	0.732 (0.725–0.739)	0.726 (0.722–0.730)	.46	0.407 (0.396–0.418)	0.417 (0.411–0.423)	.42
Anterior limb (right)	0.736 (0.729–0.742)	0.728 (0.724–0.731)	.42	0.444 (0.433–0.456)	0.455 (0.448–0.462)	.42
Posterior limb (left)	0.712 (0.706–0.717)	0.709 (0.706–0.712)	.65	0.574 (0.566–0.583)	0.582 (0.577–0.587)	.42
Posterior limb (right)	0.712 (0.707–0.718)	0.712 (0.708–0.715)	.91	0.583 (0.574–0.593)	0.590 (0.585–0.595)	.48
Retrolenticular limb (left)	0.779 (0.771–0.786)	0.774 (0.769–0.778)	.52	0.553 (0.542–0.563)	0.552 (0.546–0.558)	.95
Retrolenticular limb (right)	0.779 (0.771–0.786)	0.774 (0.769–0.778)	.52	0.553 (0.542–0.563)	0.552 (0.546–0.558)	.95
Corona radiata	0.779 (0.769–0.789)	0.752 (0.746–0.758)	.0003 ^b	0.406 (0.399–0.414)	0.421 (0.417–0.425)	.001 ^b
Anterior (left)	0.780 (0.766–0.794)	0.754 (0.745–0.762)	.0026 ^b	0.377 (0.368–0.385)	0.391 (0.386–0.396)	.007 ^b
Anterior (right)	0.793 (0.779–0.806)	0.761 (0.753–0.769)	.0003 ^b	0.394 (0.384–0.403)	0.406 (0.401–0.411)	.031 ^b
Superior (left)	0.746 (0.738–0.755)	0.721 (0.716–0.726)	.0003 ^b	0.434 (0.424–0.444)	0.452 (0.446–0.458)	.005 ^b
Superior (right)	0.741 (0.733–0.749)	0.718 (0.713–0.723)	.0003 ^b	0.435 (0.425–0.446)	0.451 (0.445–0.457)	.018 ^b
Posterior (left)	0.824 (0.813–0.835)	0.798 (0.792–0.804)	.0003 ^b	0.424 (0.412–0.435)	0.438 (0.432–0.445)	.036 ^b
Posterior (right)	0.827 (0.816–0.837)	0.801 (0.795–0.807)	.0003 ^b	0.439 (0.428–0.450)	0.456 (0.449–0.462)	.017 ^b
Posterior thalamic radiation	0.879 (0.869–0.890)	0.857 (0.851–0.863)	.0060 ^b	0.511 (0.500–0.522)	0.522 (0.515–0.528)	.12
Left	0.926 (0.910–0.941)	0.899 (0.890–0.908)	.0096 ^b	0.496 (0.483–0.508)	0.503 (0.496–0.511)	.30
Right	0.846 (0.837–0.856)	0.827 (0.822–0.833)	.0060 ^b	0.522 (0.510–0.534)	0.535 (0.528–0.542)	.087
Sagittal stratum	0.862 (0.854–0.870)	0.851 (0.846–0.856)	.11	0.432 (0.422–0.442)	0.440 (0.434–0.446)	.24
Left	0.880 (0.870–0.891)	0.867 (0.861–0.873)	.11	0.427 (0.416–0.438)	0.434 (0.428–0.440)	.36
Right	0.847 (0.839–0.855)	0.838 (0.833–0.842)	.11	0.436 (0.425–0.446)	0.445 (0.439–0.451)	.23
External capsule	0.750 (0.745–0.756)	0.748 (0.745–0.752)	.95	0.409 (0.401–0.417)	0.410 (0.405–0.414)	.95
Left	0.751 (0.746–0.757)	0.750 (0.747–0.753)	.95	0.410 (0.401–0.419)	0.412 (0.407–0.417)	.95
Right	0.749 (0.743–0.755)	0.747 (0.744–0.751)	.95	0.407 (0.399–0.415)	0.407 (0.402–0.411)	.95
Cingulum	0.790 (0.783–0.797)	0.785 (0.781–0.789)	.62	0.375 (0.364–0.386)	0.382 (0.375–0.388)	.62
Gyrus (left)	0.760 (0.752–0.768)	0.754 (0.750–0.759)	.62	0.404 (0.390–0.419)	0.419 (0.411–0.428)	.40
Gyrus (right)	0.760 (0.752–0.767)	0.750 (0.746–0.755)	.40	0.409 (0.395–0.424)	0.418 (0.410–0.426)	.62
Hippocampal (left)	0.840 (0.831–0.850)	0.839 (0.834–0.845)	.99	0.321 (0.308–0.333)	0.318 (0.311–0.325)	.99
Hippocampal (right)	0.840 (0.830–0.850)	0.839 (0.833–0.845)	.99	0.325 (0.314–0.336)	0.325 (0.318–0.331)	.99
Fornix	0.988 (0.974–1.003)	0.978 (0.969–0.986)	.56	0.431 (0.421–0.441)	0.432 (0.427–0.438)	.90
Left	0.848 (0.836–0.861)	0.853 (0.846–0.860)	.71	0.442 (0.431–0.452)	0.441 (0.435–0.447)	.93
Right	0.902 (0.889–0.915)	0.906 (0.899–0.914)	.71	0.427 (0.416–0.439)	0.423 (0.416–0.429)	.71
Superior longitudinal fasciculus	0.752 (0.744–0.759)	0.735 (0.731–0.739)	.0004 ^b	0.409 (0.400–0.417)	0.421 (0.417–0.426)	.015 ^b
Left	0.751 (0.743–0.758)	0.734 (0.730–0.739)	.0005 ^b	0.403 (0.394–0.412)	0.414 (0.409–0.419)	.040 ^b
Right	0.752 (0.745–0.760)	0.736 (0.732–0.740)	.0005 ^b	0.413 (0.404–0.422)	0.426 (0.421–0.431)	.015 ^b
Superior fronto-occipital fasciculus	0.756 (0.742–0.770)	0.724 (0.716–0.731)	.0003 ^b	0.372 (0.358–0.385)	0.394 (0.387–0.402)	.006 ^b
Left	0.761 (0.744–0.777)	0.726 (0.716–0.735)	.0008 ^b		0.385 (0.377–0.394)	.041 ^b
Right	0.749 (0.737–0.761)	0.721 (0.714–0.727)	.0003 ^b	0.377 (0.363–0.392)	0.406 (0.398–0.414)	.001 ^b
Uncinate fasciculus	0.801 (0.790–0.812)	0.793 (0.786–0.799)	.34	0.393 (0.375–0.410)	0.407 (0.397–0.417)	.34
Left	0.808 (0.794–0.822)	0.799 (0.791–0.807)	.34	0.369 (0.350–0.388)	0.381 (0.370–0.392)	.34
Right	0.794 (0.783–0.804)	0.786 (0.780–0.792)	.34	0.416 (0.398–0.434)	0.434 (0.423–0.444)	.34
Tapetum	1.284 (1.243–1.325)	1.260 (1.237–1.284)	.62	0.433 (0.416–0.450)	0.439 (0.429–0.449)	.81
Left	1.437 (1.378–1.497)	1.423 (1.389–1.458)	.81	0.400 (0.380–0.421)	0.399 (0.387–0.410)	.89
Right	1.178 (1.139–1.216)	1.148 (1.126–1.170)	.62	0.456 (0.438–0.474)	0.467 (0.457–0.477)	.62

Note:—Pont indicates Pontine.

^a P values compare the diffusion tensor imaging measures (mean diffusivity and fractional anisotropy) between survivors with persistent leukoencephalopathy and survivors without a history of leukoencephalopathy using general linear modeling, adjusted for current age. All models are corrected for false discovery rate. Survivors with persistent leukoencephalopathy had reduced white matter integrity, demonstrated by higher mean diffusivity and lower fractional anisotropy, in the corpus callosum and bilateral corona radiata, superior longitudinal fasciculi, and superior fronto-occipital fasciculi. Higher mean diffusivity indicates reduced white matter integrity in the bilateral posterior thalamic radiations.

^b Significant.

On-line Table 3: Association between persistent leukoencephalopathy and neurocognitive outcomes^a

	All (N = 173)		Persistent LE (n = 41)			No Evidence of LE (n = 121)			Group P ^c
	Mean ^b (SD)	Pop P ^c	Mean ^b (SD)	% Impaired ^d	95% CI	Mean ^b (SD)	% Impaired ^d	95% CI	
Executive function									
Flexibility	-0.53 (1.20)	<.0001	-0.62 (1.50)	32.5	(17.9–47.0)	-0.48 (1.09)	23.1	(15.4–30.7)	.71
Fluency	-0.37 (0.98)	<.0001	-0.48 (1.05)	27.5	(13.6–41.3)	-0.32 (0.97)	25.0	(17.1–32.8)	.45
Working memory	-0.30 (1.02)	<.0001	-0.38 (1.09)	20.0	(7.6–32.4)	-0.32 (0.97)	18.8	(11.7–25.8)	.80
Planning	-0.20 (1.0)	.0096	-0.22 (0.97)	12.5	(2.3–22.8)	-0.18 (1.0)	19.8	(12.6–27.1)	.75
Memory									
Span	-0.42 (1.02)	<.0001	-0.64 (0.99)	27.5	(13.6–41.3)	-0.34 (1.01)	19.6	(12.4–26.8)	.10
Processing speed									
Motor	-1.29 (1.53)	<.0001	-1.35 (1.80)	47.5	(32.0–62.9)	-1.31 (1.46)	40.1	(31.2–49.0)	.99
Visual motor	-0.40 (0.98)	<.0001	-0.50 (1.29)	30.0	(15.8–44.2)	-0.39 (0.86)	14.5	(8.1–20.9)	.52
Attention									
Focused	-0.35 (1.16)	.0001	-0.47 (1.36)	32.5	(17.9–47.0)	-0.33 (1.11)	18.8	(12.1–27.0)	.80
Sustained	-0.23 (1.38)	.0031	-0.23 (1.55)	12.5	(2.2–22.8)	-0.24 (1.28)	14.9	(8.3–21.4)	.68
Perseveration	-0.40 (1.80)	.0051	-0.37 (1.75)	17.5	(5.7–29.3)	-0.36 (1.65)	14.0	(7.6–20.4)	.45
Intelligence									
Full-scale	-0.14 (0.89)	.037	-0.17 (1.05)	15.0	(3.9–26.0)	-0.15 (0.86)	10.3	(4.8–15.8)	.84
Global neurocognitive impairment ^e				60.0	(24.9–56.7)		58.8	(32.1–50.8)	.89

Note:—Pop indicates population; LE, leukoencephalopathy.

^a“Persistent LE” refers to survivors who presented with leukoencephalopathy both during active therapy and follow-up. “No evidence” of LE refers to survivors with no leukoencephalopathy detected during active therapy and follow-up. 11 subjects had leukoencephalopathy during treatment that were not present on the follow-up MRI.

^b Group means and SDs are represented in age-adjusted z scores referenced to nationally representative norms. A lower score is indicative of worse functioning.

^c Pop P compares the group average with the expected population value ($\mu = 0, \sigma = 1.0$) for the specific tests. Group P compares mean standardized scores between survivors with leukoencephalopathy at follow-up and those without for the specific tests.

^d“Impairment” is defined as a score falling below the tenth percentile of the age-adjusted z score.

^e Global neurocognitive impairment is defined as having ≥ 2 neurocognitive tests that fall ≥ 1.5 SDs or 1 test that falls > 2 SDs below the age-adjusted population normative data.

On-line Table 4: Association between global neurocognitive impairment and white matter integrity^a

Tracts	Mean Diffusivity (95% CI)			Fractional Anisotropy (95% CI)		
	Impaired (n = 63)	Not Impaired (n = 87)	P ^b	Impaired (n = 63)	Not Impaired (n = 87)	P ^b
Corpus callosum	0.916 (0.906–0.926)	0.904 (0.896–0.913)	.096	0.529 (0.520–0.539)	0.526 (0.518–0.534)	.63
Genu	0.806 (0.794–0.818)	0.790 (0.780–0.800)	.043 ^c	0.475 (0.459–0.491)	0.474 (0.461–0.487)	.93
Body	0.935 (0.922–0.948)	0.922 (0.911–0.933)	.14	0.506 (0.494–0.518)	0.508 (0.498–0.519)	.77
Splenium	0.962 (0.948–0.975)	0.954 (0.942–0.965)	.37	0.570 (0.561–0.579)	0.563 (0.555–0.571)	.26
Corona radiata	0.767 (0.758–0.776)	0.753 (0.746–0.761)	.024 ^c	0.415 (0.409–0.421)	0.420 (0.415–0.425)	.23
Anterior (left)	0.770 (0.758–0.781)	0.753 (0.744–0.763)	.044 ^c	0.382 (0.375–0.389)	0.391 (0.385–0.397)	.069
Anterior (right)	0.778 (0.767–0.790)	0.763 (0.753–0.772)	.039 ^c	0.398 (0.390–0.405)	0.407 (0.401–0.413)	.076
Superior (left)	0.733 (0.726–0.741)	0.723 (0.717–0.729)	.039 ^c	0.447 (0.439–0.456)	0.448 (0.441–0.455)	.87
Superior (right)	0.730 (0.723–0.737)	0.719 (0.714–0.725)	.021 ^c	0.448 (0.439–0.456)	0.447 (0.439–0.454)	.82
Posterior (left)	0.810 (0.801–0.819)	0.801 (0.793–0.808)	.13	0.435 (0.426–0.445)	0.434 (0.427–0.442)	.87
Posterior (right)	0.814 (0.805–0.823)	0.803 (0.795–0.810)	.077	0.452 (0.443–0.462)	0.451 (0.443–0.459)	.81
Posterior thalamic radiation	0.864 (0.855–0.873)	0.862 (0.854–0.869)	.69	0.518 (0.509–0.527)	0.520 (0.512–0.527)	.78
Left	0.908 (0.894–0.921)	0.904 (0.893–0.915)	.71	0.501 (0.491–0.511)	0.502 (0.494–0.511)	.85
Right	0.833 (0.825–0.841)	0.832 (0.825–0.838)	.73	0.530 (0.521–0.540)	0.532 (0.524–0.540)	.76
Superior longitudinal fasciculus	0.742 (0.736–0.748)	0.737 (0.732–0.742)	.19	0.417 (0.410–0.423)	0.420 (0.414–0.425)	.51
Left	0.741 (0.735–0.747)	0.736 (0.731–0.741)	.23	0.412 (0.405–0.419)	0.412 (0.406–0.418)	.97
Right	0.743 (0.737–0.749)	0.737 (0.732–0.743)	.19	0.420 (0.413–0.427)	0.425 (0.419–0.431)	.28
Superior fronto-occipital fasciculus	0.742 (0.731–0.754)	0.725 (0.715–0.734)	.024 ^c	0.385 (0.374–0.396)	0.390 (0.381–0.399)	.48
Left	0.746 (0.732–0.760)	0.727 (0.716–0.739)	.043 ^c	0.378 (0.366–0.389)	0.381 (0.371–0.391)	.64
Right	0.738 (0.728–0.748)	0.722 (0.713–0.730)	.017 ^c	0.394 (0.382–0.405)	0.401 (0.391–0.410)	.37

^a“Global neurocognitive impairment” is defined as having ≥ 2 neurocognitive tests (listed in On-line Table 3) that fall > 1.5 SDs or 1 test that falls > 2 SDs below the age-adjusted population normative data. Survivors with neurocognitive impairment had reduced white matter integrity, demonstrated by higher mean diffusivity in the genu of the corpus callosum as well as in the bilateral corona radiata and superior fronto-occipital fasciculi. Higher mean diffusivity and lower fractional anisotropy are indicative of worse white matter integrity.

^b P values compare the mean diffusivity between survivors with and without neurocognitive impairment using general linear modeling, adjusted for current age.

^c Significant.