Published in final edited form as:

J Child Neurol. 2014 June ; 29(6): 774–781. doi:10.1177/0883073813488675.

Long-Term Outcome and Risk Factors for Uncontrolled Seizures After a First Seizure in Children With Hematological Malignancies

Raja B. Khan, MD¹, E. Brannon Morris, MD¹, Ching-Hon Pui, MD³, Melissa M. Hudson, MD³, Yinmei Zhou, MS², Cheng Cheng, PhD², Davonna S. Ledet, MS¹, and Scott C. Howard, MD³

¹ Division of Neurology, St. Jude Children's Research Hospital, Memphis, TN, USA

² Departments of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN, USA

³ Departments of Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA

Abstract

Long-term outcomes of seizures that develop during treatment of childhood hematological malignancies have not been described. We analyzed seizure outcome in 62 children with leukemia or lymphoma treated at our institution. There was a median follow-up of 6.5 years since first seizure. Seizure etiology included intrathecal or systemic methotrexate in 24, leucoencephalopathy in 11, brain hemorrhage or thrombosis in 11, meningitis in 4, and no identifiable cause in 12. Seizures remained uncontrolled in 18, and risk factors for poor control included female sex ($P = .02$), no seizure control with first antiseizure drug ($P = .08$), and longer interval between cancer diagnosis and seizure onset ($P = .09$). Poor seizure control after initial antiseizure drug also predicted recurrent seizure after drug withdrawal ($P = .04$). In conclusion, seizures are controlled with medications in a majority of patients with hematological cancer. After a period without seizures, antiseizure drug withdrawal in appropriately selected patient has a high success rate.

Keywords

leukemia; lymphoma; seizures; outcome; hematological malignancy; methotrexate

Hematological malignancies are the most common childhood cancer¹ and the treatment of acute leukemia and non-Hodgkin's lymphoma requires repeated intravenous and intrathecal

© The Author(s) 2013

Corresponding Author: Raja B. Khan, MD, Division of Neurology, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, USA. raja.khan@stjude.org.

Author Contributions

RBK conceived the project and collected the data and wrote the manuscript. EBM, CP, MMH, YZ, CC, DSL, and SCH provided guidance throughout the project, were involved in clinical care of the patients, helped in understanding the data, and edited the manuscript. YZ was responsible for statistical analyses, supervised by CC.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The Institutional Review Board approved the study; requirement for informed consent was waived because of the retrospective nature of the study and minimal risk to study subjects.

infusions of potentially neurotoxic drugs. Cognitive problems, white matter changes visible by magnetic resonance imaging (MRI) of the brain (leucoencephalopathy), and seizures are recognized complications of therapy for children with leukemia or lymphoma.²⁻⁶ Seizures have been reported to develop in up to 10% of children during leukemia treatment, though a recent large trial reported a cumulative incidence of 4.7% when no cranial radiation therapy was used.⁵⁻⁷ However, only 1 study of 17 patients describes the long-term seizure outcome and the risk factors for uncontrolled seizure in children with leukemia and lymphoma, but recurrent seizure after withdrawal of antiepilepsy drugs were not determined.⁸ The Childhood Cancer Survivor Study investigators reported a 7% incidence of seizures in acute leukemia survivors followed for 20 years after leukemia diagnosis. This determination was based on self-reported questionnaire responses, but information about the timing, severity, risk factors, and prognosis was not available.⁹ In this study, we evaluate risk factors for poor seizure control and seizure recurrence after antiseizure drug withdrawal in a large cohort of comprehensively followed pediatric patients with acute leukemia or non-Hodgkin's lymphoma.

Methods

The Institutional Review Board approved the study; the requirement for informed consent was waived because of the retrospective nature of the study and minimal risk to study subjects. Eligibility criteria included a diagnosis of acute leukemia or non-Hodgkin's lymphoma, age 18 years or younger at cancer diagnosis, at least 1 witnessed unequivocal seizure, at least 6 months of follow-up after the first seizure, no history of seizures prior to cancer diagnosis, and cancer treatment at St. Jude Children's Research Hospital from January 1985 to June 2005. During the study period, all children with acute leukemia or non-Hodgkin's lymphoma who developed seizures were followed by St. Jude neurologists, and neurology clinic records were prospectively kept for all patients with seizures. Study variables were defined prior to data collection (Tables 1 and 2), and information was abstracted from the medical record by the neurologist caring for the patients (RBK). We evaluated the number and types of seizures, presence of neurologic deficits at the time of first seizure, antiseizure drugs used, risk factors for poor seizure control, and risk factors for recurrent seizure in patients whose antiseizure drugs were stopped after achieving seizure control.

Seizures were defined according to International League Against Epilepsy classification.¹⁰ Seizure control was defined based on the number of seizures over a 6-month period preceding last clinic follow-up as controlled if there was no seizure; uncontrolled if 1 or more seizures; and intractable if 1 or more seizure each month during the 6-months period. Breakthrough seizure was defined as a seizure occurring after initial antiseizure drug therapy reached steady state (5 or more half-lives of the drug). All patients with seizure at our center are followed in the same outpatient neurology clinic, and a neurologist (RBK, EBM) assessed seizure control and adverse effects during routine clinical evaluations. Neuroimaging studies were reviewed for focal or diffuse white matter hyper intense signal change (leucoencephalopathy), and calcification at the cortical-subcortical junction (mineralizing microangiopathy; Figure 1).

Chi-square tests and logistic regression analyses were used to investigate the association between seizure outcome and associated variables. *P* values are 2-sided and were not adjusted for multiple comparisons. Multivariable analyses with backward stepwise selection were used to determine the factors that were statistically most important in their association with seizure outcome. Adjusted odd ratios were obtained from multivariable logistic regression. The log-rank test and multivariable Cox proportional hazards model were used to assess the association between uncontrolled seizures, seizure recurrence after antiseizure drug withdrawal, and associated variables.

Results

Patient Cohort

The 62 patients who fulfilled eligibility criteria had a median age of 6.4 years (range, 0.1 to 17.9 years) at diagnosis of cancer and a median age at first seizure of 9.8 years (range, 0.1 to 17.9 years). After their first seizure, patients were followed for a median of 6.5 years (range 0.5 to 20 years), and their clinical characteristics are shown in Table 1. The primary malignancy was acute lymphoblastic leukemia in 47, acute myeloid leukemia in 5, acute promyelocytic leukemia in 2, and non-Hodgkin's lymphoma in 8. During the study period 1575 leukemia and 404 non-Hodgkin's lymphoma patients were treated at our institution giving approximate seizure incidence of 3% in leukemia and 2% in lymphoma patients. In addition to systemic and intrathecal chemotherapy, 16 children were treated with cranial irradiation and 15 underwent stem cell transplantation. Central nervous system disease was present in 16 (26%) at tumor diagnosis, and tumor relapse occurred in 18 patients. At the time of data freeze, 51 patients were still alive, and 44 of these were still in active follow-up in neurology clinic.

Seizure Type and Etiology

The first seizure was a generalized tonic-clonic in 25 (40%) and complex partial in 37 (60%). Three children had status epilepticus as first seizure: generalized tonic-clonic in 1 and complex partial in 2. Probable seizure etiology could be determined in 50: intrathecal or high-dose systemic methotrexate within 10 days prior to seizure in 24 (39%); leucoencephalopathy 11 (18%); intracranial hemorrhage 6 (10%); intracranial venous sinus thrombosis 5 (8%); and meningitis 4 (6%). Although some patients had more than 1 potential cause of seizure, the primary cause was determined by the treating neurologist. In 12 cases, no specific cause was identified after thorough evaluation, including neurologist evaluation and MRI imaging of the brain for all patients, and electroencephalogram in 51 cases.

Timing of First Seizure

The median time from cancer diagnosis to first seizure was 0.54 years (range, 0 to 13.5 years); 25% of seizures occurred within 1.5 months of diagnosis and 75% within 15.5 months (Figure 2). Thirty-three patients (53%) had only a single seizure before antiseizure drug therapy was initiated, and the remaining 29 received antiseizure drug therapy only after subsequent seizures. The initial antiseizure drug was gabapentin in 27, phenytoin in 18, carbamazepine in 8, phenobarbital in 5, and valproic acid in 4. Of 62 children, 34 (55%) had

at least 1 breakthrough seizure after starting antiseizure drug therapy, and 25 (40%) had 3 or more breakthrough seizures. Twenty-nine of the 34 children with breakthrough seizures were on a medication with routinely available serum drug levels; 2 were subtherapeutic, 5 low therapeutic, 11 high therapeutic, and 4 supratherapeutic.

Seizure Control

At last follow-up, seizures were controlled in 44 patients and uncontrolled in 18. Of the 21 patients that had controlled seizures and were taking antiseizure drugs, 11 were taking gabapentin, 5 topiramate, 2 each of valproic acid and levetiracetam, and 1 was on carbamazepine. Of these 21, everyone except 9 taking gabapentin were treated initially with a different antiseizure drug. Of the 23 patients taking no antiseizure drug at the last follow-up, 20 were treated with single antiseizure drug: gabapentin in 14, valproic acid in 3, carbamazepine in 2, and phenobarbital in 1. Another 3 taking no antiseizure drug at last follow-up were initially treated with gabapentin, phenobarbital, and valproic acid respectively and were eventually controlled with carbamazepine in 1 and gabapentin in the other 2.

A number of variables were associated with uncontrolled seizures in univariable analysis (Table 1), but in multivariable analysis, only female gender achieved significance for $P < .05$. Lack of seizure control with first antiseizure drug used and seizures not developing in early induction period trended toward reaching significance ($P = .08$ and $.09$, respectively). Intractable seizures were present in 10 patients at the time of last follow-up. Age younger than 3 years at cancer diagnosis and presence of central nervous system leukemia correlated with intractable seizures.

Seizure Recurrence After Antiepilepsy Drug Withdrawal

Antiseizure drugs were withdrawn in 32 patients after a variable period of seizure control (from 6 to >24 months); 24 patients had no recurrent seizure and 8 had recurrence (Table 2). The median time from first seizure to antiseizure drug withdrawal was 1.8 years (range, 0.11 to 12.2 years) and the median follow-up time after antiseizure drug withdrawal was 2.7 years (range, 1.0 to 19 years). A median of 2.2 years (range, 0.77 to 9.6 years) passed between antiseizure drug withdrawal and recurrent seizure in the 8 patients with recurrence. In univariable analysis, risk factors for recurrence included use of an antiseizure drug other than gabapentin, no response to the initial antiseizure drug, cranial radiation therapy, and mineralizing microangiopathy (Table 2). However, in multivariable analysis, only lack of response to the initial antiseizure drugs remained statistically significant ($P = .04$; Table 3).

Final Seizure Outcome

At last follow-up, 23 (37%) patients remained seizure-free off antiseizure drugs, 21 (34%) had seizures controlled on antiseizure drugs, and 18 (29%) had uncontrolled seizures. Of the 18 with uncontrolled seizures, 10 (16% of all 62 patients) had intractable seizures.

Electroencephalogram (EEG)

EEG results were available for 51 patients. Reports were not present in the charts of 11, and we could not determine the reason. Diffuse slowing of the background rhythm was seen in 6,

focal slow waves in 13 and focal sharp or spike waves in 37 patients. Pre-antiseizure drug withdrawal EEG was available in 30 of 32 patients. Diffuse background slowing was present in 1, focal slow waves in 5, and focal sharp or spike waves in 21 patients.

Discussion

Methotrexate treatment was the most common underlying cause of seizures in this cohort. We started treating first seizure with antiseizure drugs in children with cancer after we realized a high risk of subsequent seizures during the course of treatment. Although we show good long-term control of seizures with appropriate drug management, we do not have data to show benefit of early versus delayed treatment with antiseizure drugs. However, we demonstrate good long-term seizure control in majority of these patients and subsequent successful withdrawal of antiseizure drugs in appropriately selected patients.

Age younger than 3 years at the time of tumor diagnosis was the single most important factor predicting poor seizure outcome on univariable analyses. It correlated with intractable refractory epilepsy unresponsive to multiple medications on multivariable analyses as well. A newborn's brain is poorly myelinated and myelination of the whiter matter proceeds rapidly in the first 3 years of life. However, many additional years are required to complete the process.¹¹ Thus, brain in earlier years of maturation may be more vulnerable to toxic effects of cancer treatment. This is also suggested by more profound cognitive problems in children diagnosed with cancer at younger age and treated with chemo or radiation therapy.¹² However, we could not confirm age association with uncontrolled seizures on multivariable analyses. It is possible that there may be true lack of correlation between younger age at tumor diagnosis and poor seizure outcome, or relatively small cohort and interaction with other variables may have prevented it from gaining statistical significance on multivariable analyses.

There were many other variables which predicted poor seizure control status on univariable analyses (Table 1), but none of these achieved statistical significance on multivariable regression analyses except female gender. A higher predisposition to neurotoxicity from chemotherapy and radiation therapy is well recognized in females and is largely unexplained.^{13,14} Lack of response to first antiseizure drug and longer time interval between first seizure and cancer diagnosis trended toward reaching significance ($P = .08$ and $.09$). Lack of response to first antiseizure drug is a recognized poor prognostic marker in epilepsy patients without cancer,¹⁵ and likely represents a structural injury rather than chemical toxicity. Longer time interval from cancer diagnosis may also reflect seizure development because of structural brain injury from cancer or its treatment, contrary to early onset seizures where transient neuronal dysfunction from high dose chemotherapy during induction phase may be the seizure trigger.

Majority of the seizures occurred within first 6-months of cancer treatment (Figure 2) and may be an explanation of overall good outcome. Maytal et al⁸ in their cohort of 17 patients found neurologic deficits to be predictor of poor seizure outcome, a finding that we did not confirm in this study. Likewise, we could not confirm leukemia recurrence as a risk factor for developing epilepsy as reported by Childhood Cancer Survivor Study.⁹ However,

inclusion of a high proportion (29%) of relapsed patients in this study may have confounded the analyses.

Many anticancer drugs are metabolized by hepatic enzyme system (cytochrome P450 3A4) and an earlier study from our institution suggested lower event-free survival in children with leukemia whose seizures were treated with hepatic enzyme inducing antiseizure drugs.¹⁶ Marked reduction in serum levels of certain chemotherapy agents have been demonstrated in phase-I studies when used concurrently with enzyme inducing antiseizure drugs.^{17,18} This results in requiring much higher dose of chemotherapy agents, increased cost, and still less reliable serum levels. Recognition of the interaction made us switch to gabapentin monotherapy for patients with new-onset seizures as the drug does not induce hepatic enzymes, does not bind to serum proteins, and has no known clinically relevant interaction with chemotherapeutic agents. Gabapentin use was associated with better seizure control than other agents in univariable analysis ($P = .002$) but less strongly in multivariable analysis ($P = .055$). Although not approved for monotherapy by the FDA, this drug is included in the list of medications for use as monotherapy for new-onset localization related seizures in adults in the American Epilepsy Society and American Academy of Neurology guidelines.¹⁹ We have previously reported its successful use in children with brain tumors,²⁰ and the current study also suggests usefulness of gabapentin in children with hematologic cancers. Our data cannot be used to compare different antiseizure drugs since this study was neither randomized nor controlled. Gabapentin is considered by some to be of relatively lower potency compared to other antiseizure drugs. We did experience breakthrough seizures in some children treated with gabapentin and addressed that by incrementing the dose, at times to higher than conventional dose when tolerated. This may explain our success with this drug. In the past few years levetiracetam—another anti-seizure drug with no hepatic enzyme induction—has become the drug of choice for many neurologists treating seizures in patients with cancer. We also now use levetiracetam as initial treatment of seizure because of its ease of use, less frequent dosing, and availability of intravenous formulation.

Antiseizure drug withdrawal was attempted in half the patients. Mineralizing microangiopathy, treatment with cranial radiation therapy, and lack of response to first antiseizure drug correlated on univariable analyses with recurrent seizures after drug withdrawal, but only lack of seizure control after initial antiseizure drug therapy was an independent risk factor on multivariable regression analysis. These findings are not surprising since many of the risk factors identified in univariable analysis are highly correlated with each other, such as central nervous system leukemia with cranial radiation therapy and age less than 3 years, and younger age and cranial radiation therapy with mineralizing microangiopathy. For example, the presence of mineralizing microangiopathy suggests a more severe neurologic injury and presence of central nervous system leukemia may predispose to calcium deposition in a growing nervous system, and certainly increases the likelihood of needing cranial radiation therapy.

The seizure relapse rate of 25% after antiseizure drug withdrawal is similar to that reported in the literature for children without a history of cancer.²¹ However, about half of the patients who developed recurrent seizures after antiseizure drug withdrawal did so after 12

months of completing the withdrawal. It is thus possible that more patients would have developed recurrent seizure if there was longer than 2.7 years median follow-up. Conventional risk factors for seizure recurrence after antiseizure drug withdrawal such as multiple seizures prior to diagnosis, older age at seizure onset, and focal slow or sharp waves on EEG did not correlate with seizure relapse risk.^{21,22} Our study is the first to report mineralizing microangiopathy as a risk factor for seizure recurrence, though it did not predict recurrence independently of other variables. Correlation of lack of response to first antiseizure drug with seizure recurrence after drug withdrawal on multivariable analyses is consistent with literature reports of higher seizure relapse rate in children who had more difficult to control seizures.^{15,23}

Although our study spans almost 2 decades, patients were evaluated by the same 2 neurologists, and standardized neurologic information recorded as part of routine care. This study has a small number of patients when compared to studies of idiopathic epilepsy in children. However, considering overall low prevalence of childhood cancer and a low risk of seizures in hematological malignancies, this study represents a very large cohort. The relatively small number of patients and multiple study variables, many of which were correlated with each other, may also confound our results. We employed stepwise regression analyses to overcome this weakness, but this cannot completely compensate for the relatively small sample size.

Conclusions

Seizures in children with leukemia and lymphoma often recur if no antiseizure drug is prescribed after a first seizure, but can usually be controlled with antiseizure drugs that do not induce hepatic enzymes. Some patients require long-term antiseizure drug use, but a trial of antiseizure drug withdrawal is reasonable in patients with controlled seizures, since most will remain seizure-free at 5 years after withdrawal, and even those with recurrence may enjoy a seizure-free interval off medication.

Acknowledgements

These data were presented at the 2007 Child Neurology Society annual meeting held in Quebec City, Quebec.

Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: Supported in part by grant P30 CA-21765 and Cancer Center Core Grant CA 21765 from the National Institutes of Health, a Center of Excellence grant from the state of Tennessee, and the American Lebanese Syrian Associated Charities (ALSAC). Dr Pui is the American Cancer Society F.M. Kirby Professor.

References

1. Howlader, N.; Noone, AM.; Krapcho, M., et al. SEER Cancer Statistics Review, 1975-2008. National Cancer Institute; Bethesda, MD: 2010. Available at http://seer.cancer.gov/csr/1975_2008/
2. Iuvone L, Mariotti P, Colosimo C, et al. Long-term cognitive outcome, brain computed tomography scan, and magnetic resonance imaging in children cured for acute lymphoblastic leukemia. *Cancer*. 2002; 95:2562–2570. [PubMed: 12467071]

3. Reddick WE, Shan ZY, Glass JO, et al. Smaller white-matter volumes are associated with larger deficits in attention and learning among long-term survivors of acute lymphoblastic leukemia. *Cancer*. 2006; 106(4):941–949. [PubMed: 16411228]
4. Raymond-Speden E, Tripp G, Lawrence B, Holdaway D. Intellectual, neuropsychological, and academic functioning in long-term survivors of leukemia. *J Pediatr Psychol*. 2000; 25:59–68. [PubMed: 10820944]
5. Ochs JJ, Bowman WP, Pui CH, et al. Seizures in childhood lymphoblastic leukaemia patients. *Lancet*. 1984; 2:1422–1424. [PubMed: 6151043]
6. Mahoney DH Jr, Shuster JJ, Nitschke R, et al. Intensification with intermediate-dose intravenous methotrexate is effective therapy for children with lower-risk B-precursor acute lymphoblastic leukemia: A Pediatric Oncology Group study. *J Clin Oncol*. 2000; 18:1285–1294. [PubMed: 10715299]
7. Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. *N Engl J Med*. 2009; 360:2730–2741. [PubMed: 19553647]
8. Maytal J, Grossman R, Yusuf FH, et al. Prognosis and treatment of seizures in children with acute lymphoblastic leukemia. *Epilepsia*. 1995; 36:831–836. [PubMed: 7635103]
9. Goldsby RE, Liu Q, Nathan PC, et al. Late-occurring neurologic sequelae in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2010; 28:324–331. [PubMed: 19917844]
10. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on classification and terminology of the International League Against Epilepsy. *Epilepsia*. 1989; 30(4):389–399.
11. Bird CR, Hedberg M, Drayer BP, et al. MR assessment of myelination in infants and children: usefulness of marker sites. *Am J Neuroradiol*. 1989; 10:731–740. [PubMed: 2505502]
12. Kingma A, Mooyaart EL, Kamps WA, et al. Magnetic resonance imaging of the brain and neuropsychological evaluation in children treated for acute lymphoblastic leukemia at a young age. *Am J Pediatr Hematol Oncol*. 1993; 15:231–238. [PubMed: 8498647]
13. von der Weid N, Mosimann I, Hirt A, et al. Intellectual outcome in children and adolescents with acute lymphoblastic leukaemia treated with chemotherapy alone: age- and sex-related differences. *Eur J Cancer*. 2003; 39:359–365. [PubMed: 12565989]
14. Waber DP, Tarbell NJ, Kahn CM, et al. The relationship of sex and treatment modality to neuropsychologic outcome in childhood acute lymphoblastic leukemia. *J Clin Oncol*. 1992; 10:810–817. [PubMed: 1569453]
15. Tripathi M, Padhy UP, Vibha D, et al. Predictors of refractory epilepsy in north India: a case-control study. *Seizure*. 2011; 20(10):779–783. [PubMed: 21821437]
16. Relling MV, Pui CH, Sandlund JT, et al. Adverse effect of anti-convulsants on efficacy of chemotherapy for acute lymphoblastic leukaemia. *Lancet*. 2000; 356:285–290. [PubMed: 11071183]
17. Gilbert MR, Supko JG, Batchelor T, et al. Phase I clinical and pharmacokinetic study of irinotecan in adults with recurrent malignant glioma. *Clin Cancer Res*. 2003; 9:2940–2949. [PubMed: 12912940]
18. Kargiotis O, Markoula S, Kyritsis AP. Epilepsy in the cancer patient. *Cancer Chemother Pharmacol*. 2011; 67:489–501. [PubMed: 21305288]
19. French JA, Kanner AM, Bautista J, et al. Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology; Quality Standards Subcommittee of the American Academy of Neurology; American Epilepsy Society. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004; 62:1252–1260. [PubMed: 15111659]
20. Khan RB, Hunt DL, Boop FA, et al. Seizures in children with primary brain tumors: incidence and long-term outcome. *Epilepsy Res*. 2005; 64:85–91. [PubMed: 15941651]
21. Specchio LM, Beghi E. Should antiepileptic drugs be withdrawn in seizure-free patients? *CNS Drugs*. 2004; 18:201–212. [PubMed: 15015901]

22. Hauser E, Freilinger M, Seidl R, Groh C. Prognosis of childhood epilepsy in newly referred patients. *J Child Neurol*. 1996; 11:201–204. [PubMed: 8734022]
23. Verrotti A, D'Egidio C, Agostinelli S, et al. Antiepileptic drug withdrawal in childhood epilepsy: what are the risk factors associated with seizure relapse? *Eur J Paediatr Neurol*. 2012; 16(6):599–604. [PubMed: 22398177]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1. Central nervous system lesions in selected patients with seizures. A and B: Computed tomography images show calcification consistent with microangiopathy (arrows) in 2 patients with seizures. Panels C and D: T2-weighted MRI images show diffuse hyperintense signal in the white matter consistent with leucoencephalopathy (arrows) in 2 patients with seizures.

Figure 2.
Seizure onset in relation to cancer diagnosis.

Table 1

Univariable Exact Logistic Regression Analysis for Risk Factors of Uncontrolled Seizures (n = 62).

Factors	Numbers	Odds Ratio (%95 CI)	P Value
Age at tumor DX			
3 vs >3 years	20 vs 42	8.6 (2.2, 37.8)	.0008
Gender			
Male vs female	35 vs 27	0.3 (0.07, 0.9)	.04
DX category			
ALL vs AML + APL + NHL	47 vs 15	0.164 (0.3, 5.9)	1.0
Leukemia relapse			
Yes vs no	18 vs 44	2.7 (0.7, 10.1)	.2
BMT			
Yes vs no	15 vs 47	1.9 (0.5, 7.7)	.4
Presence of CNS leukemia			
Yes vs no	16 vs 46	5.1 (1.3, 21.5)	.02
Leucoencephalopathy			
Yes vs no	21 vs 41	0.3 (0.05, 1.3)	.1
Cause of seizure			
Intrathecal or high-dose methotrexate vs other	24 vs 38	0.3 (0.07, 1.4)	.2
History of thrombus			
Yes vs no	7 vs 55	0.4 (0.008, 3.5)	.7
# of seizures prior to starting AED			
Single vs = 2	33 vs 29	0.8 (0.2, 2.9)	.9
Use of seizure drug other than gabapentin			
Gabapentin vs other	27 vs 35	0.09 (0.01, 0.5)	.002
Response to first AED			
Yes vs no	38 vs 24	0.1 (0.03, 0.5)	.002
Presence of focal neurologic deficits			
Present vs absent	9 vs 53	3.7 (0.7, 22.0)	.1
Time first SZ from diagnosis	62	1.0 (1.0, 1.05)	.02
Treatment with radiation			
Yes vs no	16 vs 46	5.1 (1.3, 21.5)	.02
Mineralizing microangiopathy			
Yes vs no	8 vs 54	5.1 (0.9, 37.3)	.08
Focal slow waves on EEG	51		
Present vs absent	13 vs 38	5.0 (1.1, 24.9)	.04
Spike waves on EEG	51		
Present vs absent	37 vs 14	0.9 (0.2, 5.0)	1.0

Abbreviations: AED, antiepilepsy drug; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; APL, acute promyelocytic leukemia; BMT, bone marrow transplant; CI, confidence interval; CNS, central nervous system; DX, diagnosis; EEG, electroencephalogram; NHL, non-Hodgkin's lymphoma; SZ, seizure; vs, versus.

Table 2

Univariable Exact Logistic Regression for Risk Factors of Seizure After AED Withdrawal (n = 32).

Factors	Numbers	Odds Ratio (%95 CI)	P Value
Age at tumor diagnosis			
3 vs >3 years	6vs26	3.9 (0.4, 40.0)	.30
Gender			
Male vs female	20 vs 12	1.0 (0.1, 8.0)	1.0
Diagnosis category			
ALL vs AML + APL + NHL	24 vs 7	1.0 (0.1, 12.7)	1.0
Leukemia relapse			
Yes vs no	6 vs 26	0.6 (0.01, 6.4)	1.0
Intrathecal or high-dose methotrexate vs others	16 vs 16	0.5 (0.07, 3.4)	.7
Bone marrow transplant			
Yes vs no	3 vs 29	0.7 (0.0, 7.5)	.8
Presence of CNS leukemia			
Yes vs no	5 vs 27	0.7 (0.01, 9.2)	1.0
Leucoencephalopathy			
Yes vs no	13 vs 19	0.4 (0.03, 2.9)	.5
History of thrombus			
Yes vs no	7 vs 25	0.4 (0.01, 4.8)	.8
# of seizures prior to starting AED			
Single vs > = 2	17 vs 15	3.4 (0.5, 41.3)	.3
Use of seizure drug other than gabapentin			
Gabapentin vs other	17 vs 15	0.08 (0.001, 0.8)	.02
Response to first AED			
Yes vs no	24 vs 8	0.09 (0.01, 0.8)	.02
Presence of focal neurologic deficits			
Present vs absent	4 vs 28	12.3 (0.8, 754.5)	.08
Time first seizure from diagnosis	32	1.05 (1.0, 1.2)	.3
Treatment with radiation			
Yes vs no	6 vs 26	9.9 (1.04, 145.1)	.05
Mineralizing microangiopathy			
Yes vs no	3 vs 29	14.8 (1.4, Infinity)	.02
Focal slow waves on EEG	30		
Present vs absent	5 vs 25	2.1 (0.1, 22.9)	.8
Spike waves on EEG	30		
Present vs absent	21 vs 9	1.4 (0.2, 17.4)	1.0

Abbreviations: AED, antiepilepsy drug; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; APL, acute promyelocytic leukemia; CI, confidence interval; CNS, central nervous system; EEG, electroencephalogram; NHL, non-Hodgkin's lymphoma; vs, versus.

Table 3

Multivariable Exact Logistic Regression Analyses of Risk Factors for Uncontrolled Seizures and Seizure After Antiseizure Drug Withdrawal.

Variable	P Value	Odds Ratio (95% CI)
Uncontrolled seizures		
Gender (male vs female)	.02	0.18 (0.04, 0.77)
Gabapentin vs other AED	.06	0.16 (0.02, 1.11)
Seizure control with first AED vs no control	.08	0.26 (0.06, 1.15)
Longer vs short interval from DX to first seizure	.09	1.02 (0.99, 1.04)
Intractable seizures		
Age <3 vs ≥3 years at cancer diagnosis	.01	9.6 (1.6, 56.8)
CNS leukemia at diagnosis vs normal CNS	.02	0.1 (0.02, 0.69)
Seizure relapse after AED withdrawal		
Seizure control with first AED vs no control	.04	−2.7 (−5.2, −0.2)
Focal neurologic deficit present vs absent	.08	3.1 (−0.3, 6.4)
Radiation treatment vs no treatment	.05	2.5 (−0.3, 5.3)

Abbreviations: AED, antiepilepsy drug; CNS, central nervous system; DX, diagnosis; vs, versus.