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Advanced Stage Anaplastic Large Cell Lymphoma in Children and Adolescents: Results of ANHL0131, a Randomized Phase III Trial of APO Versus a Modified Regimen with Vinblastine: A Report from the Children's Oncology Group

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Abstract

Background—Optimal therapy for children and adolescents with advanced stage anaplastic large cell lymphoma (ALCL) is unknown. ANHL0131 examined whether a maintenance regimen including vinblastine compared to the standard APO (doxorubicin, prednisone, vincristine, methotrexate, 6-mercaptopurine) regimen would result in superior event-free survival.

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Procedure—125 eligible patients were enrolled. Induction was identical for both arms. Post induction patients were randomized to receive APO with vincristine every 3 weeks or a regimen that substituted vincristine with weekly vinblastine (APV).

Results—There was no difference between the patients randomized to the APO versus APV arms in either event free survival (EFS) or overall survival (OS) (3 year EFS 74% versus 79%, $p=0.68$ and 3 years OS of 84% versus 86%, $p=0.87$, respectively). Patients in the APV arm required dose reduction secondary to myelosuppression and had a higher incidence of neutropenia as well as infection with neutropenia compared to those in the APO arm ($P<0.001$, $p=0.019$, respectively).

Conclusions—Treatment with weekly vinblastine instead of every three week vincristine as part of multi-agent maintenance therapy did not result in improvement in EFS or OS. Weekly vinblastine was associated with increased toxicity. ([ClinicalTrials.gov Identifier NCT00059839](https://clinicaltrials.gov/ct2/show/study/NCT00059839))

Keywords

anaplastic large cell lymphoma; vinblastine

Introduction

Anaplastic large cell lymphoma (ALCL) accounts for 10–15% of all pediatric non-Hodgkin Lymphoma (NHL).^{1,2} ALCL is characterized by large pleomorphic cells of T/null cell phenotype that are strongly CD30 positive. In the World Health Organization Classification ALCL is divided into anaplastic lymphoma kinase (ALK) positive and ALK negative disease.^{3–5} In children, more than 90% of ALCL is ALK positive, due, in the majority of cases, to a translocation $t(2;5)(p23;q35)$ involving the *ALK* gene on chromosome 2 and the *NPM* gene on chromosome 5. A minority of ALCL cases have alternative ALK translocation partners.^{6,7}

The majority of pediatric patients with ALCL present with advanced stage disease, with almost all having nodal involvement and 30–50% having mediastinal disease.^{8–10} Extranodal disease is also common including involvement of bone, bone marrow, lung, skin and other soft tissues. Central nervous system involvement is rare. In patients with advanced disease, 50% will have B symptoms at presentation.

The most effective treatment regimen for children with advanced stage ALCL has not been established. Various therapeutic strategies have been investigated in cooperative group trials including the use of short intensive pulse chemotherapy lasting 4–6 months^{8–12} and acute lymphoblastic leukemia-like or repeated pulse prolonged therapy^{13–17} Despite the variations in duration and intensity, the EFS in pediatric patients with ALCL is remarkably consistent across studies with approximately 30% of patients continuing to experience disease progression or recurrence within 2 years of diagnosis.^{8,10,11,16}

One of the unique features of ALCL compared to other pediatric non-Hodgkin lymphomas, is its sensitivity to chemotherapy after recurrence, suggesting that an active agent added to front line therapy may be able to reduce the relapse rate. A regimen of single agent weekly vinblastine has been shown to be highly effective for pediatric patients with relapsed ALCL,

with the majority obtaining a second complete remission and a smaller number achieving long-term remissions with this therapy alone.^{18,19} Given the activity of this agent in the relapsed setting, vinblastine was investigated as a component of therapy for newly diagnosed pediatric patients with ALCL in a cooperative group trial in Europe and in this Children's Oncology Group trial.¹¹

The APO regimen (doxorubicin, prednisone, vincristine, 6-mercaptopurine and methotrexate) has been shown to be an effective and safe in a series of Pediatric Oncology group studies.^{16,20} The primary aim of this study was to determine whether the addition of weekly vinblastine to the APO regimen following induction would result in a superior event free survival for children with advanced stage ALCL.

Methods

Patients

Eligible patients were less than 21 years old with newly diagnosed CD30+ Murphy Stage III or IV ALCL. Patients could not have received prior therapy except for those treated with limited irradiation or steroids for emergent management of a mediastinal mass. Adequate liver and cardiac function was required. Patients with disease limited to skin, pregnant patients and those with B cell phenotype lymphoma were not eligible. Written informed consent was obtained from all patients in accordance with federal and local institutional review board guidelines and the Declaration of Helsinki.

Treatment

Randomization occurred at the time of patient enrollment. (Fig 1) Induction therapy was identical in the two arms and consisted of doxorubicin 75 mg/m² on days 1 and 22, vincristine 1.5 mg/m² (maximum dose 2 mg) on days 1, 8, 15, 22 and 29, prednisone 40 mg/m² daily for 28 days, and age adjusted intrathecal methotrexate on days 1, 8, and 22. Maintenance started on day 43 and consisted of 15 cycles given every 21 days for an approximate total duration of therapy of 12 months. Based on their assignment by randomization, patients were treated with either standard APO maintenance (doxorubicin 30 mg/m² day 1(cycles 1–5), methotrexate 60 mg/m² day 1 (cycles 6–15), vincristine 1.5 mg/m² day 1, prednisone 120 mg/m² on days 1–5 and 6-Mercaptopurine 225 mg/m² on days 1–5) or with APV maintenance in which vinblastine 6 mg/m² (maximum dose 6.7mg) on days 1, 8, and 15 was substituted for the day 1 vincristine. Both maintenance arms included intrathecal (IT) methotrexate on day 1 of maintenance cycles 1 to 3. Patients with central nervous system disease received five additional doses of IT methotrexate as well as 2400 cGy cranial radiation.

Stringent criteria for dose reductions of vinblastine were included in the protocol including: 1) delay in therapy due to hematopoietic toxicity (ANC<500/ μ L or platelets <75,000/ μ L) resulting in greater than four weeks between the initiation of maintenance cycles (i.e. greater than a one week delay); 2) inability to administer either the second or third dose (days 8 or 15, respectively) of vinblastine because of myelotoxicity (absolute neutrophil count (ANC)

less than 500 μ L); 3) nadir of ANC less than 200 μ L at any time; 4) Grade III or IV neuropathic pain; or 5) other Grade III or IV toxicities attributed to vinblastine.

The study began with a vinblastine dose of 6 mg/m² but there were targeted toxicity monitoring rules which directed a reduction in the starting dose of vinblastine (first to 5 mg/m² and then again to 4 mg/m² if necessary) should excess toxicity be observed. The protocol directed that the study be closed to enrollment should the 4 mg/m² vinblastine dose be too toxic.

Pathology

Pathologic central review was completed by two independent reviewers (MCK, SLP) for all patients for whom materials were received using the diagnostic criteria set forth in the 2001 WHO Classification⁵ that was being used at the time of the start of the protocol and reanalyzed to incorporate definitions set forth in the 2008 WHO Classification³ The final pathologic review used for data analysis was based on WHO 2008 criteria. Morphologic analysis included sub-classification into common versus other subtypes (small cell variant, lymphohistiocytic, monomorphic, Hodgkin-related and NOS) subtypes.⁴ All cases were assigned to a specific morphologic subcategory according to criteria in the 2008 WHO Classification with the addition of a monomorphic variant, which was composed of sheets of uniform large cells without significant anaplasia, classic “Hallmark cells” or inflammatory cells such as histiocytes. The tumor cells in those tumors designated a monomorphic variant were large and monomorphic appearing with moderate amounts of clear to slightly basophilic cytoplasm and variably prominent nucleoli, but all were uniformly strongly positive for CD30 and ALK by immunohistochemistry. A few cases were placed in a not otherwise specified (NOS) category when very small biopsy size, significant crush artifact or sample type (i.e. pleural fluid) did not allow for morphologic assignment to be made with confidence. Only those patients for whom central review was conducted were included in the analysis of histology as a predictive factor of event-free survival. Central review was performed on morphologic and reference laboratory immunophenotypic analysis. Immunohistochemical staining was centrally performed for CD30 (Dako), ALK-1 (Dako), The B-cell antigen CD20 (Dako), T-cell antigens (CD3 (Novocastro), CD45RO-(Zymed), CD43 (Ventana) and TIA-1 (Beckman Coulte) in all cases. Additional staining with CD2, CD4, CD5, CD7, or CD8 (all from Novocastro) was performed in a small subset of cases that lacked expression of any of the above mentioned T-cell markers to document T-cell lineage). Cases were considered indeterminate phenotype if only non-lineage specific markers, such as CD43, were positive and/or no definitive T-cell antigen expression could be detected).

Response criteria

Complete response (CR) was defined as disappearance of all evidence of disease. Complete response, unconfirmed (CRu), was defined as a residual lymph node mass > 1.5 cm that regressed by >75% in the sum of the products of the greatest perpendicular diameters (SPD) or any residual lesions in organs that decreased by >75% with a negative gallium scan and/or PET scan. Partial response (PR) was defined as a 50% decrease in the SPD of the lesions with no new lesions. Disease response was assessed at end of induction (week 6).

For those with PR at end of induction, disease was re-assessed after one cycle of maintenance (week 9) and if not in CR/Cru a biopsy was requested.

Statistical Methods

Patients were randomized at study entry. The primary endpoint for this study was event-free survival (EFS) defined as the time from study entry until the first occurrence of disease progression, relapse after response, or death from any cause. Events occurring during induction treatment were counted against the randomized treatment. Secondary endpoints included overall survival (OS), defined as the time from study entry until death from any cause. Time to event for patients not experiencing an event was censored at their time of last follow-up. Only eligible patients were included in the outcome analyses.

The expected two-year EFS for study patients, based on the outcome for the Children's Cancer Group study CCG-5941, was 75%.¹⁷ The study was designed to randomize a minimum 200 patients and be analyzed after 55 events occurred, where events are defined as disease progression, relapse after response, or death from any cause. With a minimum follow-up of 2 years, this would provide 80% power (testing at the 5% level of statistical significance) to detect a 12% improvement (to 87%) in the two-year EFS with APV consolidation. Interim analyses were performed to assess early evidence for superiority of APV over standard APO and for evidence that the available data were inconsistent with the improved outcome with APV that the study was designed to detect.²¹ These interim analyses were performed every 6 months beginning after the 10th protocol event was observed using repeated one-sided log-rank tests. The upper critical values were based on a one-sided t^2 monitoring boundary and using an alpha-spending function approach; the lower critical values were based on testing the alternative hypothesis at a p-value of 0.005. Interim monitoring was also conducted to detect differences in toxicity rates.

Patient and pathologic characteristics and toxicities were summarized with frequencies and percentages. The toxicity rates for the more common toxicities during consolidation were compared between treatment arms with a time to first occurrence analysis using cumulative incidence methods. The log-rank test was used to compare the toxicity cumulative incidence between treatment arms. EFS and OS distributions were estimated using the Kaplan-Meier method. Comparison of time-to-event distributions by treatment arm was done using the log-rank test. Univariate analysis of prognostic factors of EFS and OS was conducted using Cox regression. Significant predictors from the univariate analysis were included in backward selection multivariate model of EFS using Cox regression, with predictors with p-values less than 0.05 retained in the model. A landmark analysis was conducted including patients undergoing disease evaluation at induction. Briefly, landmark analysis includes patients who were alive, on study, and evaluated as a CR, CRu, PR, at the end of induction. For the landmark analysis, EFS was defined as time from date of response assessment to the first occurrence of disease progression, relapse after response, or death from any cause; the EFS distribution was estimated using the Kaplan-Meier method and distributions compared by response using the log-rank test. P-values less than 0.05 were considered to be statistically significant. SAS software Version 9.2 was used for data analysis (SAS Institute Inc., Cary, NC). The data used for this analysis were those available April 1, 2010.

Results

There were 129 patients enrolled from January 2004 to December 2008. The study was closed to accrual when, at scheduled interim analysis, it was clear that the de-escalated vinblastine dose of 4 mg/m² would meet toxicity monitoring rule for further de-escalation and the protocol specified stopping accrual if the dose fell below 4 mg/m². In addition, this interim analysis suggested that a significant difference in event free survival between the two randomized treatments was unlikely. Four patients were deemed ineligible, three because pathologic review revealed Hodgkin lymphoma and one because therapy was initiated prior to consent being signed. Of the 125 eligible patients 64 were randomized to the APO arm and 61 to the APV arm.

The clinical characteristics by randomized groups are presented in Table I. The mean age of the patients was 11.9 years and the male to female ratio was 1.5:1. The majority of the patients had Murphy stage III disease.

Pathologic central review was completed for 114/129 patients (88%). Ninety percent of the patients had ALK positive disease. Disease characteristics as defined by central review are presented in Table I.

Outcomes

The 3-year EFS for all patients was 76% (95% CI of 67–83%) and the 3-year OS was 85% (95% CI of 76–91%) (Fig 2). For the patients randomized to the standard APO arm the 3-year EFS and OS were 74% (95% CI of 61–84%) and 84% (95% CI of 69–92%), respectively, compared to 79% (95% CI of 65–87%) and 86% (95% CI of 73–93%), respectively, for those on the vinblastine arm.

Response assessment was performed at the end of induction. The complete response rate (CR and CRu) was 62% in both arms. Evaluation of the association between radiographic response to induction therapy and EFS showed a trend towards improved outcomes for those with a CR/CRu as compared to those with a PR ($p=0.060$) (Fig 3). Of the 19 patients who did not obtain a CR/CRu at end induction and post the first cycle of maintenance, ten underwent re-biopsy and 2 had histologic evidence of disease.

Toxicity

The initial vinblastine dose was 6 mg/m². Of the first 20 patients enrolled at this dose, 15 required a dose reduction secondary to myelosuppression. As prescribed by the protocol the dose of vinblastine was reduced to 5 mg/m². Of the subsequent 25 patients enrolled at 5 mg/m², 17 required a dose reduction and therefore the starting dose of vinblastine for all patients was further reduced to 4 mg/m². Sixteen patients were enrolled at this dose and 9 of the 16 required further dose modifications. The median vinblastine dose for all patients enrolled on the vinblastine arm was 4 mg/m².

In general both regimens were tolerated well. Greater hematologic toxicity was seen, however, in patients receiving vinblastine. The cumulative incidence of neutropenia (absolute neutrophil counts $<1000/\text{mm}^3$) was significantly higher in the APV arm compared

to the APO arm (84% versus 39%, $p < 0.0001$). In addition, the cumulative incidence of infection with neutropenia or febrile neutropenia was significantly higher in the APV arm than in the APO arm (43% versus 22%, $p = 0.019$). There were no reported deaths from infection on therapy in either arm. The rate of sensory neuropathy was higher in the APV arm compared to the APO arm (9% versus 0%, respectively, $p = 0.031$). The frequency of additional toxicities was very low in both arms.

Prognostic factors

Prognostic factors of EFS were evaluated for the entire cohort of patients in univariate analysis. (Table II) By multivariate analysis, factors associated with a significantly worse EFS were black race (black vs. non-black: HR=4.5, 95% CI of 1.9 – 11.0, $p = 0.0009$), mediastinal involvement (yes vs. no: HR=2.6, 95% CI of 1.1 – 6.4, $p = 0.036$) and evidence of small cell variant (SCV) histology, either as a primary pattern or with significant evidence of a SCV histology admixed with other histologic subtypes (SCV vs. common: HR=14.3, 95% CI of 5.3 – 39.0; Other vs. common: HR=2.9, 95% CI of 0.9 – 8.7, $p < 0.0001$). The estimated EFS and OS distributions by histology are presented in Figure 4.

Discussion

For a number of years the treatment approach for children with newly diagnosed ALCL in North America has been based on the APO protocol, a 12 month outpatient regimen which avoids the use of alkylating agents and epipodophyllotoxins but gives anthracycline to a total cumulative dose of 300 mg/m². By contrast, the BFM study group utilized a short-pulse inpatient chemotherapy regimen with treatment duration of 4–6 months depending on stage. This regimen includes high dose methotrexate and alkylating agents, with a lower cumulative dose of anthracycline. Despite these differences both strategies demonstrate an approximately 30% incidence of relapse or progressive disease. Randomized trials evaluating modifications of these regimens^{10,16} have failed to demonstrate an impact on EFS or OS.

Following demonstration that weekly vinblastine is an effective agent for patients with relapsed ALCL,¹⁹ randomized trials in Europe and North America were designed to test whether the addition of this drug to standard therapy would improve outcome. The ANHL0131 study examined whether EFS could be improved for patients with advanced stage ALCL by the substitution of weekly vinblastine for every three week vincristine in the maintenance portion of the APO regimen. The results showed that the addition of weekly vinblastine to the APO backbone increased toxicity but did not improve EFS with a three year EFS of 76% for all patients registered on study.

The 3 year EFS of 76% is similar to that found in the recently conducted European Trial ALCL-99 which reported a two year EFS of 74% for all patients and 71% in the higher risk group.^{10,11} Patients with higher risk disease on the ALCL-99 trial were randomized to the addition of vinblastine to five chemotherapy courses followed by weekly vinblastine for a total of one year of therapy or to standard therapy with no additional vinblastine and no maintenance. ALCL-99 demonstrated the addition of vinblastine delayed relapses in the first year, but did not improve the 2-year EFS. The time to relapse was 13.1 months in the

vinblastine treatment arm compared to 6.5 months in the no-vinblastine arm with no difference found in the time from last chemotherapy injection to relapse in the two arms. This suggests that the length of therapy, rather than the addition of vinblastine, resulted in the longer first remission duration. This finding is in concordance with other studies in which the median time to relapse was 26 months when the therapy duration was 24 months¹⁵ and 8.5 months with short duration therapy¹² with no change in EFS (65% at 8.4 years and 68% at 5 years, respectively).

In the present study the administration of weekly vinblastine in combination with conventional chemotherapy was associated with an increased incidence of toxicity including peripheral neuropathy and myelosuppression. The starting dose of vinblastine was sequentially reduced from 6mg/m² to 5 mg/m² and then to 4 mg/m² based on protocol criteria. The median vinblastine dose for the maintenance cycles was 75% of the initial starting dose. This is comparable to the dose tolerated in the ALCL-99 study when vinblastine was given as a single drug in maintenance, with a mean dose of vinblastine reported of 78% of the planned 6 mg/m² weekly dose.¹⁰

Several factors associated with an increased risk of relapse were identified in this trial including mediastinal involvement, black race, and non-classical histology. Mediastinal disease, which is present in 30–50% of patients at diagnosis, has been identified as a poor prognostic factor previously.²²

Black race was associated with lower EFS, which has not previously been described in pediatric ALCL. The association of race and ethnicity with outcomes in various other pediatric hematologic malignancies has been described in the literature with variable results.^{23–25}

Small cell variant histology was highly associated (P <0.001) with adverse outcome in our cohort, which replicates the prognostic significance of variant histologies reported in the ALCL-99 trial and the poor prognosis reported in the original description.^{26,27}

Other robust prognostic indicators at the time of diagnosis for children with ALCL are the level of NPM-ALK transcripts in bone marrow determined by quantitative RT-PCR and level of antibody titers to ALK in plasma.^{28,29} “Biological risk stratification” utilizing both NPM-ALK transcripts in bone marrow and ALK antibody titers in plasma at the time of diagnosis was able to stratify patients into high, intermediate, and low risk groups with progression-free survivals of 93%, 68% and 28%, respectively (P<0.0001).³⁰

Finding novel ways to improve the outcome for children with ALCL, especially those at higher risk, are needed. Intensification of methotrexate and cytosine arabinoside^{10,16}, utilization of a compressed T cell regimen¹⁷, and now incorporation of vinblastine have all failed to improve the EFS¹¹. Preliminary results of studies utilizing novel biologically targeted agents such as brentuximab vedotin (SGN-35), an antibody drug conjugate combining an anti-CD30 antibody with a potent microtubule inhibitor, monomethylauristatin (MMAE), and crizotinib a small molecule inhibitor of the ALK tyrosine kinase, appear to be very promising in terms of efficacy and safety.^{31–34} Plans for evaluating the effect of adding brentuximab vedotin and crizotinib to standard chemotherapy

in newly diagnosed patients with ALK positive ALCL are being pursued by the Children's Oncology Group.³⁵

In conclusion, results of COG study ANHL0131 demonstrate that replacement of vincristine with weekly vinblastine in APO maintenance therapy had no impact on EFS or OS in pediatric patients with advanced stage ALCL. Despite the activity of vinblastine as a single agent in children with relapsed ALCL,¹⁹ the optimal strategy for its use and its utility in upfront therapy remains to be defined. Clinical trials designed to validate risk factors for relapse and/or progressive disease and which evaluate the efficacy of biologically targeted agents, including brentuximab vedotin and crizotinib, are critical next steps in the ongoing attempts to improve the outcome of children with ALCL.

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Figure 1.
Chemotherapy schema

Figure 2.
Event free (a) and overall survival (b) by treatment arm

Figure 3.

Figure 4.
Event free (a) and overall survival (b) by histologic subtype

Table I

Patient characteristics and centrally reviewed pathology compared between the randomized groups

	Total	ARM A APO	ARM B APV
Patient characteristics	N=125	N=64	N=61
Age in years, median (range)	11.9 (0.7 – 20.0)	11.2 (3.0 – 20.0)	13.2 (0.7 – 19.6)
Male	74 (59%)	38 (61%)	34 (56%)
Ethnicity and Race			
Hispanic/Latino	18 (14%)	10 (16%)	8 (13%)
Non-Hispanic/Latino	103 (82%)	51 (80%)	52 (85%)
Unknown	4 (3%)	3 (5%)	1 (2%)
White	87 (70%)	46 (72%)	41 (67%)
Asian	8 (6%)	5 (8%)	3 (5%)
Black/African American	18 (14%)	7 (11%)	11 (18%)
Unknown	12 (10%)	6 (9%)	6 (10%)
Murphy stage			
Stage III	98 (78%)	52 (84%)	48 (79%)
Stage IV	27 (22%)	10 (16%)	13 (21%)
CNS involvement	4 (3%)	1 (2%)	3 (5%)
BM involvement	14/114 (12%)	7/59 (12%)	7/55 (13%)
Mediastinal involvement	57 (46%)	29 (45%)	28 (46%)
Extranodal involvement	54 (43%)	22 (34%)	32 (52%)
“B” symptoms	72 (58%)	34 (53%)	38 (62%)
Centrally reviewed pathology	N=114	N=59	N=55
ALK status			
Positive	101 (90%)	51 (91%)	49 (91%)
Negative	10 (9%)	5 (9%)	5 (9%)
Indeterminate	1 (1%)	0 (0%)	0 (0%)
Unavailable	2	1	1
Immunophenotype			
Indeterminate/Null	15 (13%)	7 (13%)	8 (15%)
T-Cell	98(86%)	51(86%)	47 (85%)

	Total	ARM A APO	ARM B APV
Unavailable	1	1	0
Histologic Subtype			
Common	74 (65%)	39 (66%)	35 (64%)
Monomorphic	7 (6%)	4 (7%)	3 (5%)
Small Cell Variant	20 (18%)	8 (14%)	12 (22%)
Lymphohistiocytic	4 (4%)	3 (5%)	1 (2%)
Hodgkin related	4 (4%)	2 (3%)	2 (4%)
NOS	5 (4%)	3 (5%)	2 (4%)

CNS: central nervous system, BM: bone marrow, "B" symptoms: temperature >38°C for 3 consecutive days, night sweats or unexplained weight loss of more than 10 % in prior 6 months; ALK: anaplastic lymphoma kinase, NOS: not otherwise specified

Table II

Univariate predictors of outcome for all patients

		Event-free survival		Overall survival	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age	< 12 years	1		1	
	≥12 years	2.21 (0.99 – 4.93)	0.047	2.87 (0.91 – 9.04)	0.059
Gender	Male	1		1	
	Female	0.68 (0.31 – 1.52)	0.34	1.15 (0.42 – 3.18)	0.79
Ethnicity	Other	1		1	
	Hispanic	1.06 (0.37 – 3.05)	0.92	1.40 (0.39 – 4.95)	0.60
Race	White	1		1	
	Black	2.85 (1.22 – 6.68)	0.030	3.03 (0.99 – 9.28)	0.11
	Other	0.89 (0.26 – 3.06)		1.02 (0.22 – 4.83)	
Murphy stage	Stage III	1		1	
	Stage IV	1.20 (0.48 – 2.97)	0.70	2.82 (1.00 – 7.95)	0.040
Mediastinal involvement	No	1		1	
	Yes	2.69 (1.21 – 6.00)	0.012	3.51 (1.12 – 11.03)	0.022
Extranodal involvement	No	1		1	
	Yes	1.01 (0.47 – 2.16)	0.98	1.44 (0.52 – 3.98)	0.48
“B” symptoms	No	1		1	
	Yes	1.36 (0.62 – 2.97)	0.44	2.16 (0.69 – 6.79)	0.19
Histologic Subtype	Common	1		1	
	SCV	13.1 (5.06 – 33.8)	<0.0001	17.1 (4.21 – 69.1)	<0.0001
	Other	3.35 (1.12 – 9.96)		5.46 (1.22 – 24.5)	