Clinical characteristics and treatment outcomes of children with anaplastic large cell lymphoma: a single center experience

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Background
Anaplastic large cell lymphoma (ALCL) is uncommon in children, accounting for approximately 15% of all cases of childhood non-Hodgkin lymphoma. Despite many studies attempting new treatment strategies, treatment outcomes have not significantly improved, and the optimal treatment for pediatric ALCL has not been established.

Methods
The records of newly diagnosed ALCL patients at our institute between July 1998 and April 2013 were reviewed. We evaluated the general characteristics of the patients, chemotherapy regimens, overall survival (OS) rates, and event-free survival (EFS) rates.

Results
Twenty-eight ALCL patients were eligible. The median age at diagnosis was 10.8 years. Lymph node involvement was the most common presentation (79%). CCG-5941, a multi-agent T-cell lineage chemotherapy, was the predominant treatment regimen (57%). The five-year OS and EFS rates were 88% and 69%, respectively. Stage, the presence of B symptoms, lung involvement, and bone marrow involvement were significant prognostic factors for EFS (P=0.02, 0.01, 0.01, and 0.02, respectively). Eight patients relapsed, and three died during the study period. Four of the eight patients who relapsed were treated with high-dose chemotherapy and autologous stem cell transplantation (HDCT-ASCT). Two of the four who had undergone HDCT-ASCT developed secondary relapses and were subsequently treated with allogeneic SCT or brentuximab.

Conclusion
We found that treatment outcomes with multi-agent chemotherapy in children with ALCL were similar to those of previous reports, and that relapsed patients could be salvaged with HDCT-ASCT or allogeneic SCT. A prospective, larger cohort study is warranted to define the optimal treatment for pediatric ALCL.

Key Words
Anaplastic large cell lymphoma, Childhood, Prognosis, Relapse

INTRODUCTION

Anaplastic large cell lymphoma (ALCL), which is characterized by the proliferation of anaplastic cells of the T or null phenotype [1], is a rare disease in children accounting for about 15% of childhood non-Hodgkin lymphomas (NHL) [2]. ALCL has a broad morphological spectrum characterized by the infiltration of pleomorphic cells in a sinusoidal pattern and co-expression of Ki-1 or CD30 epithelial membrane antigen and the interleukin-2 receptor [3, 4]. ALCL is referred to as “large cell anaplastic lymphoma” in the revised Kiel classification, and it is a subgroup of the peripheral T-cell lymphomas in the Revised European-American Lymphoma (REAL) classification [5, 6]. The definition of ALCL has recently been further refined; in the 2008 World Health Organization (WHO) classification of lymphoma, ALCL is classed as a subtype of the mature T-cell and NK-cell neoplasms [7].

Despite recent advances in its characterization, the optimal treatment of ALCL has not been established, and the efficacy and safety of treatments are still under investigation [8].
Most European pediatric oncology groups report successful outcomes for ALCL patients treated with an intensive short-pulse chemotherapy regimen based on B-cell NHL-type therapy [9-11]. In contrast, several other pediatric oncology groups treat ALCL patients with less-intensive but prolonged, repeated-pulse therapy [1, 12-14]. In a number of studies, the event-free survival (EFS) rate ranged from 60% to 75%, and relapse occurred in up to 35% of patients [1, 10, 12, 14, 15]. For relapsed patients, various second-line treatments ranging from vinblastine alone to high-dose chemotherapy with hematopoietic stem cell transplantation (HSCT) have been investigated, but there is currently no consensus on the optimal treatment strategy [16-18]. Approximately 50% of patients with refractory disease will relapse again, and they have limited treatment options, such as palliative chemotherapy, radiotherapy, allogeneic SCT, or experimental approaches [19, 20]. Recently, new, targeted therapies such as brentuximab or crizotinib have shown impressive results in clinical trials treating relapsed patients with ALCL [21-23].

Although the first study regarding the clinical features and treatment outcomes of Korean pediatric patients with ALCL (N=5) was published in 1995 [24], there have been very few studies reported since. We have, therefore, analyzed the clinical characteristics and treatment outcomes of children newly diagnosed with ALCL at a single center in Korea.

## RESULTS

### Clinical characteristics

The demographic and clinical characteristics of the 28 patients are detailed in Table 1. Of the 28 patients, 19 (68%) were male. The median age of the patients was 10.8 years (range, 1.4–16 years). According to the St Jude’s classification, 2 (7%) patients had stage I disease, 6 (21%) had stage II, 15 (53%) had stage III, and 5 (18%) had stage IV. Lymph node involvement was present in 79% of patients at diagnosis. Of the 18 (64%) patients presenting with extranodal involvement, mediastinal involvement was the most common (N=9). B symptoms occurred as initial symptoms in 14 patients (50%). A serum LDH level >500 IU/L was noted in 17 patients (61%). All patients had a T-cell or null cell phenotype on immunohistochemistry. Eighteen patients (64%) had a T-cell phenotype. The ALK status was available for only 18 patients, and of them, 12 were positive.

### Treatment results

All 28 patients received combination chemotherapy. Twenty-three (82%) patients achieved complete remission (CR). Of the five patients (18%) who did not achieve CR, three had progressive disease with treatment, and two had a partial response. Of the three patients with progressive disease, two patients had stage III disease and one had stage IV disease with bone marrow involvement. The two patients who achieved a partial response were treated with further chemotherapy.

Eight of the 28 patients (28%) relapsed (Table 2). The median time to relapse from diagnosis was 12.5 months with...
Table 1. Demographic and clinical characteristics of 28 pediatric ALC patients.

| Characteristics | N (%) |
|----------------|-------|
| Age at diagnosis (year) | Median age 10.8 (1.4–16) |
| < 10 year | 13 (46) |
| ≥ 10 year | 15 (54) |
| Gender | Male 19 (68) Male 9 (32) |
| Stage I | 2 (7) |
| II | 6 (21) |
| III | 15 (53) |
| IV | 5 (18) |
| Lymph node involvement | 22 (79) |
| Extranodal involvement | 18 (64) |
| Skin | 0 |
| Lung | 4 |
| Mediastinum | 9 |
| Other viscera | 8 |
| Bone | 4 |
| CNS | 1 |
| Bone marrow | 4 |
| B symptoms | Absent 14 (50) Present 14 (50) |
| ALK status | Negative 6 (21) Positive 12 (43) Not done 10 (36) |
| Serum LDH level | ≤ 500 IU/L 17 (61) > 500 IU/L 11 (39) |

Abbreviations: CNS, central nervous system; ALK, anaplastic lymphoma kinase; LDH, lactate dehydrogenase.

Table 2. Characteristics and outcomes of relapsed patients.

| No. | Stage at initial diagnosis | Time of relapse from diagnosis (months) | Salvage therapy | Outcome |
|-----|---------------------------|----------------------------------------|-----------------|---------|
| 3   | IV                        | 21                                     | LSA2-L2         | Alive 17 years post-relapse |
| 10  | III                       | 26                                     | HDCT-ASCT       | Alive 7.8 years post-relapse |
| 15  | III                       | 25                                     | CCG-1882        | Died 17 months post-relapse due to treatment-related cause |
| 19  | III                       | 6                                      | Mod.COG ANHL06P1 | Died 4 months post-relapse due to disease progression |
| 20  | IV                        | 3                                      | Mod.COG ANHL06P1 | Died 3 months post-relapse due to disease progression |
| 21  | III                       | 2                                      | HDCT-ASCT       | 2nd relapse treated with allogeneic SCT |
| 23  | IV                        | 6                                      | HDCT-ASCT       | 2nd relapse treated with brentuximab and allogeneic SCT |
| 25  | III                       | 19                                     | Brentuximab, HDCT-ASCT | Alive 21 months post-1st relapse |

Abbreviations: HDCT-ASCT, high-dose chemotherapy-autologous stem cell transplantation; SCT, stem cell transplantation; CCG, Children’s Cancer Group; COG, Children’s Oncology Group.
Table 3. Prognostic factors for overall survival and event-free survival rates (log-rank test).

| Factors                      | 5-year OS rate | P  | 5-year EFS rate | P  |
|------------------------------|----------------|----|-----------------|----|
| Age at diagnosis             |                |    |                 |    |
| < 10 years                   | 74%            | 0.05| 65.8%           | 0.78 |
| ≥ 10 years                   | 100%           |    | 70.9%           |    |
| Gender                       |                |    |                 |    |
| Male                         | 80%            | 0.88| 76.7%           | 0.18 |
| Female                       | 88.9%          |    | 51.9%           |    |
| Stage                        |                |    |                 |    |
| I                            | 100%           | 0.59| 100%            | 0.02 |
| II                           | 100%           |    | 100%            |    |
| III                          | 86.2%          |    | 66.7%           |    |
| IV                           | 80%            |    | 60%             |    |
| Serum LDH                    |                |    |                 |    |
| ≤ 500 IU/L                   | 90.9%          | 0.83| 61.8%           | 0.34 |
| > 500 IU/L                   | 85.6%          |    | 79.5%           |    |
| B symptoms                   |                |    |                 |    |
| Yes                          | 85.7%          | 0.49| 47.6%           | 0.01 |
| No                           | 90.9%          |    | 90.9%           |    |
| ALK status                   |                |    |                 |    |
| Yes                          | 71.4%          | 0.25| 41.7%           | 0.08 |
| No                           | 100%           |    | 100%            |    |
| Lymph node involvement       |                |    |                 |    |
| Yes                          | 90.9%          | 0.68| 75.6%           | 0.17 |
| No                           | 80%            |    | 41.7%           |    |
| Extranol involvement         |                |    |                 |    |
| Yes                          | 80.8%          | 0.17| 63.6%           | 0.35 |
| No                           | 100%           |    | 77.8%           |    |
| Lung                         |                |    |                 |    |
| Yes                          | 75%            | 0.37| 25%             | 0.01 |
| No                           | 89.8%          |    | 76.4%           |    |
| Other viscera                |                |    |                 |    |
| Yes                          | 83.3%          | 0.82| 71.4%           | 0.88 |
| No                           | 90.5%          |    | 67.3%           |    |
| Bone                         |                |    |                 |    |
| Yes                          | 75%            | 0.44| 50%             | 0.50 |
| No                           | 91.7%          |    | 72.9%           |    |
| CNS                          |                |    |                 |    |
| Yes                          | 100%           | 0.72| 100%            | 0.13 |
| No                           | 87.4%          |    | 71.7%           |    |
| Mediastinum                  |                |    |                 |    |
| Yes                          | 88.9%          | 0.93| 77.8%           | 0.84 |
| No                           | 87.4%          |    | 65.6%           |    |
| Bone marrow                  |                |    |                 |    |
| Yes                          | 75%            | 0.11| 50%             | 0.02 |
| No                           | 90.8%          |    | 73.3%           |    |
| Protocol                     |                |    |                 |    |
| CCG-5941                     | 83.3%          | 0.64| 70%             | 0.95 |
| Others                       | 91.7%          |    | 74.1%           |    |
| Relapse                      |                |    |                 |    |
| Yes                          | 56.3%          | 0.003| 70%             | 0.95 |
| No                           | 100%           |    | 74.1%           |    |

Abbreviations: OS, overall survival; EFS, event-free survival; LDH, lactate dehydrogenase; ALK, anaplastic lymphoma kinase; CNS, central nervous system.

Fig. 1. Overall survival (OS) and event-free survival (EFS) rates of 28 patients with anaplastic large cell lymphoma (A). OS and EFS rates of eight relapsed patients (B).
DISCUSSION

The definition of ALCL has recently been reappraised, and options for its treatment are still under investigation. Our retrospective review of 28 patients diagnosed with ALCL in a single center contributes to the establishment of the clinical features, outcomes, prognostic factors, and treatments of refractory childhood ALCL in Korea. Among diverse factors, stage, the presence of B symptoms, and lung or bone marrow involvement were prognostic factors affecting EFS. Of the eight patients who relapsed, three died and five patients were alive after salvage therapy including HDCT-ASCT, brentuximab, and allogeneic SCT.

Various treatment strategies from short-pulse B-cell lineage NHL-type chemotherapy to prolonged lymphoblastic lymphoma/leukemia-type therapy have been the subject of many trials of several pediatric oncology groups; however, the optimal treatment for pediatric ALCL has not yet been established. In our study, the five-year OS and EFS rates for the total cohort of 28 pediatric ALCL patients were 88% and 69%, respectively, and more than a half of the patients were treated with CCG-5941, a chemotherapy protocol designed for T-cell lineage lymphoblastic leukemia. This result was comparable to those of previous studies. In the BFM group, ALCL was treated according to the short-pulse chemotherapy strategy proven to be efficacious for mature B-cell NHL. In an analysis of the BFM group trial NHL-BFM 90, Seidemann et al. [10] reported a five-year EFS rate of 76% for 89 patients with newly diagnosed ALCL. Thirty-four patients treated with the AIEOP LNH 92 protocol, which is based on a modified LSA2-L2 acute leukemia protocol, showed a 10-year EFS of 65%. The treatment consisted of an induction of a remission phase, followed by consolidation and maintenance for a total duration of 24 months [12]. The CCG-5941 protocol was a compressed aggressive multi-agent T-cell lineage chemotherapy regimen consisting of three weeks of induction therapy, followed by a three-week consolidation period followed by six courses of maintenance chemotherapy every seven weeks; for 86 patients with systemic ALCL treated with CCG-5941 the five-year EFS rate was 68% [14]. Although many studies, including our own, have found that leukemia-type chemotherapy regimens result in successful treatment outcomes, there is still no consensus on the optimal treatment for pediatric ALCL.

In conclusion, despite being limited by the small number of patients, our study has shown that treatment outcomes are not uniform. Therefore, we have a limited ability to evaluate whether the treatment regimen has an effect on outcomes.

In our study, treatment regimens were left to the physician’s discretion; therefore, the treatment regimens or criteria were not uniform. Therefore, we have a limited ability to evaluate whether the treatment regimen has an effect on outcomes.

In conclusion, despite being limited by the small number of patients, our study has shown that treatment outcomes with multi-agent chemotherapy in Korean children with ALCL are similar to those of previous Western reports, and that relapsed patients can be salvaged with HDCT-ASCT or allogeneic SCT. Further investigation of the role of new, targeted therapies is warranted for relapsed pediatric patients.

Authors’ Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.
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