Aggressive Natural Killer Cell Leukemia: A Brief Overview of Its Genomic Landscape, Histological Features, and Current Management

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Abstract

Aggressive natural killer-cell leukemia (ANKL) is a rare hematological malignancy characterized by the abnormal proliferation of natural killer (NK) cells. There are currently no therapies approved by the US Food and Drug Administration (FDA) for the treatment of ANKL, but advancements in genomics are assisting in the unraveling of this rare malignancy. We selected 37 articles that contained information on genomics, immunohistochemistry, and/or current clinical trials relating to the treatment and survival of ANKL. Current therapeutic strategies have been subdivided into (1) concurrent chemoradiation, (2) sequential chemoradiation, and (3) sandwich chemoradiation. These methods have been developed to reduce toxicity while still producing a pathologic response. Concurrent chemoradiation with VIDL (etoposide, ifosfamide, dexamethasone, and L-asparaginase) produced an excellent clinical response, while sequential chemoradiation with SMILE (steroid dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) showed an adequate response, but with severe hematologic toxicity. The efficacy of L-asparaginase in chemotherapeutic regimens and its association with NK-cell apoptosis have led to its inclusion in all standard regimens. Future studies are focusing on the addition of a programmed death-ligand 1 (PD-L1) inhibitor and hematopoietic stem cell transplant (HSCT).

Categories: Genetics, Oncology, Hematology
Keywords: natural killer cells, epstein barr virus, leukemia, ankl, aggressive natural killer cell leukemias(ankl)

Introduction And Background

Aggressive natural killer-cell leukemia (ANKL) is a rare hematological malignancy characterized by the abnormal proliferation of natural killer (NK) cells. In the 2016 World Health Organization (WHO) classification, ANKL is classified as a type of "Mature T and NK neoplasm" and has an association with the Epstein-Barr Virus (EBV) [1]. Males are twice as likely as females to be diagnosed with ANKL, with an age distribution that favors older populations, except for young adult Asian males [2-5]. The median overall survival (mOS) of ANKL is seven months, with decreasing survival rates from 45% to 31% from one year to five years, respectively [5]. Racial disparities exist in survival as African American patients are more likely to have poorer outcomes [5]. Although there are currently no therapies approved by the US Food and Drug Administration (FDA) for the treatment of ANKL, advancements in the field of genomics have considerably assisted scientists in better understanding this malignancy. Here, we present a brief overview of ANKL with consideration of its genomic landscape and histologic features, with a discussion of the current treatment regimens and the challenges experienced in the treatment of this aggressive, deadly disease.

Review

Methods

The two authors conducted the informal search on November 1, 2021, via PubMed, Science Direct, Google Scholar, and Clinical Trials search engines. The following keywords were used for the review: ‘natural killer cell leukemia’ and ‘ANKL’ (Table 1).

| Keyword                          | PubMed | ScienceDirect | Google Scholar |
|----------------------------------|--------|---------------|----------------|
| Aggressive natural killer-cell leukemia | 609    | 3.978         | 1,690          |
| ANKL                             | 63     | 168           | 1,800          |

**TABLE 1: Number of articles per search engine for specific terms**
The selected articles were basic science, clinical research, or translational research papers. Studies were included if they fulfilled any of the following criteria: (1) scientific papers written in English between 2010 and 2021; (2) published in vivo or in vitro studies evaluating the genomics of ANKL; (3) published clinical research which evaluated chemotherapeutic regimens and their impact on progression-free survival. The majority of articles that were removed did not contain information on etiology, treatment, or outcomes. After a screening process that removed duplicate articles, a total of 37 articles were selected for this review as they contained information on the genetic landscape, immunohistochemistry, and/or current clinical trials. Eight of these articles evaluated current chemoradiation therapy and progression-free survival and are summarized in Table 2.

### Table 2: A review of current treatment regimens in ANKL with corresponding survival

| Study, year | Regimen | Patients (n) | Included drugs | PFS |
|-------------|---------|--------------|----------------|-----|
| Concurrent chemoradiation | | | | |
| Yamaguchi et al. [6] | DeVIC | 27 | Dexamethasone, etoposide, ifosfamide, carboplatin | 57%, 5-year |
| Michot et al. [7] | ESHAP | 13 | Etoposide, steroid, Ara-C, cisplatin | 72%, 2-year |
| Tsai et al. [8] | DEP/DVIP | 33 | Dexamethasone, etoposide, cisplatin/dexamethasone / etoposide, ifosfamide, cisplatin | 60%, 5-year |
| Weekly cisplatin with radiation followed by chemotherapy | | | | |
| Kim et al. [9] | VIDL | 30 | Etoposide, ifosfamide, dexamethasone, L-asparaginase | 73%, 5-year |
| Sequential chemoradiation | | | | |
| Kwong [10] | SMILE | 17 | Dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide | NA |
| Dong et al. [11] | DICE-L | 33 | Cisplatin, ifosfamide, etoposide, dexamethasone, L-asparaginase | 89%, 5-year |
| Sandwich chemotherapy | | | | |
| Wang et al. [12] | GELOX/PGEMOX | 27 | Gemcitabine, L-asparaginase, oxaliplatin/pegaspargase, gemcitabine, oxaliplatin | 86%, 2-year |
| Li et al. [13] | GELOXD/GEMOXD | 167 | Gemcitabine, L-asparaginase, oxaliplatin, dexamethasone/pegaspargase, gemcitabine, oxaliplatin, dexamethasone | 73%, 5-year |

**PFS**: progression-free survival

The table is adapted from Kim et al. [14], Journal of Hematology-Oncology 2018.

### Discussion

**Etiology**

The exact etiology of ANKL remains poorly understood because it is an extremely rare entity. The Epstein-Barr virus (EBV) seems to play an important role in the pathobiology of this malignancy and is thought to be one of many factors responsible for its aggressive nature [15]. It is postulated that the EBV aids neoplastic NK cells in avoiding activated cytotoxic T-cells via a type I latency pattern of infection [16]. Surprisingly, a few cases of EBV-negative ANKL have also been reported. Unlike EBV-positive ANKL, EBV-negative ANKL tends to occur in middle-aged adults and does not display a racial preference [17,18]. Otherwise, EBV-negative ANKL patients possess similar symptoms and clinical courses as their EBV-positive counterparts [17].

**Genomic Landscape**

Preliminary results obtained by Song et al. indicated EBV-positive ANKL cells were susceptible to mutations in various immunodeficiency genes such as FANCA p.S1088F, TGFB2 p.T315M, IRF7 p.K446R, PRF1 p.R4C.
shown to selectively lead to apoptosis in NK cells due to its depletion of tumor essential L-asparagine and ifosfamide were found to be unaffected by P-glycoprotein drug resistance.

Elderly and frail patients. Etoposide had proven efficacy in EBV-related NK lymphoma but had severe hematologic toxicity, which led to the recommendation of its avoidance in ifosfamide, L-asparaginase, and etoposide.

Sequential chemoradiation began with the creation of SMILE (steroid dexamethasone, methotrexate, and L-asparaginase) showed a pathologic complete response of 87% with progression-free survival at five years of 73%.

ESHAP (etoposide, steroid, Ara-C, and cisplatin) and DEP, both of which were somewhat unsuccessful. With the modest success of DeVIC, concurrent chemoradiation was further explored with (3) sandwich chemoradiation, in which chemoradiation is followed by additional cycles of chemotherapy. With the modest success of DeVIC, concurrent chemoradiation was further explored with ESHAP (etoposide, steroid, Ara-C, and cisplatin) and DEP, both of which were somewhat unsuccessful secondary to hematologic toxicity.

Current Treatments and Clinical Trials

Traditionally, ANKL treatment consisted of anthracycline-containing chemotherapy followed by local radiation therapy of at least 45 Gy [29]. This regimen was the standard of care for locally aggressive NK-T-cell lymphomas. However, the utilization of this regimen in ANKL resulted in poor five-year survival rates (30–40%), effectively showing that these aggressive phenotypes did not respond to anthracyclines.

This resistance is hypothesized to be secondary to high concentrations of P-glycoprotein, a known resistance factor to anthracycline therapy. There is a significant obstacle, which led to the development of new chemotherapeutic regimens (Table 2).

Treatment has mostly been subdivided into three techniques: (1) concurrent chemoradiation, (2) sequential chemoradiation, and (3) sandwich chemoradiation, in which chemoradiation is followed by additional cycles of chemotherapy. With the modest success of DeVIC, concurrent chemoradiation was further explored with ESHAP (etoposide, steroid, Ara-C, and cisplatin) and DEP, both of which were somewhat unsuccessful secondary to hematologic toxicity.

Sequential chemoradiation began with the creation of SMILE (steroid dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) [29,30]. Patients treated with SMILE had an excellent 90% response rate but had severe hematologic toxicity, which led to the recommendation of its avoidance in elderly and frail patients. Etoposide had proven efficacy in EBV-related NK lymphoma.

Methotrexate and ifosfamide were found to be unaffected by P-glycoprotein drug resistance. L-asparaginase was shown to selectively lead to apoptosis in NK cells due to its depletion of tumor essential L-asparagine.
The efficacy of L-asparaginase prompted inclusion in several combination regimens, including AspaMetDex (L-asparaginase, methotrexate, and dexamethasone), VIDL (etoposide, ifosfamide, dexamethasone, and L-asparaginase), and DICE (cisplatin, ifosfamide, etoposide, dexamethasone, and L-asparaginase) [3,31-33].

Sandwich chemoradiation combines the concept of sequential chemoradiation followed by additional chemotherapy. This technique has the additional benefit of reducing the intensity of the delivered chemoradiation, which was hypothesized to decrease the toxicity effects seen in other techniques. Wang et al. showed no clinically significant late-onset toxicities in their patients, and their cohort appreciated a two-year survival rate of 86% [12]. Similarly, Li et al. analyzed this technique across three separate Chinese facilities and showed a three-year survival rate of 73%, with only 23% of patients experiencing high-grade leukopenia [13].

It remains unclear which approach, if any, is best as the risk of relapse remains a challenging issue. Recently, Song et al. evaluated the efficacy and toxicity profiles of chemoradiation followed by autologous stem cell transplantation (aSCT) in newly diagnosed advanced ANKL [34]. This study found that VIDL induction with concurrent aSCT was effective with an overall response rate of 74% and mild hematologic toxicity. However, high rates of disease recurrence with secondary relapses in the CNS (67%) have highlighted the need for CNS prophylactic therapies such as methotrexate.

Novel Therapeutic Approaches

Dufva et al. [21] proved that targeting the Janus kinase signal transducer and activator of transcription (JAK-STAT) pathway of malignant NK cells via JAK inhibitors (ruxolitinib) and the BCL-2 inhibitor, venetoclax, allowed for synergistic effects and improved drug sensitivity. Heat shock protein (HSP) 90 inhibitors, polo-like kinase (PLK), cyclin-dependent kinase inhibitors, and histone deacetylase inhibitors were also shown to be effective targets for treatment.

The polycomb repressive complex 2 (PRC2) receptor is a multiprotein complex that is involved in targeting genes for epigenetic silencing [35]. JAK/STAT pathways may play a role in the overexpression of MYC, which then interacts with PRC2 signaling histone modification [56]. This finding may suggest a novel therapeutic target.

A current study [37] by New York Medical College and the University of Alabama at Birmingham is evaluating patients with advanced-stage NK lymphoma, NK leukemia, or peripheral T-cell lymphoma in two separate cohorts. Cohort 1 will be treated with a modified SMILE regimen (dexamethasone, methotrexate, ifosfamide, pegaspargase, and etoposide) and pembrolizumab. Cohort 2 will combine pralatrexate (PRX) and brentuximab vedotin (BV) with cyclophosphamide, doxorubicin, and prednisone. Both groups will then undergo allogeneic stem cell transplants. The study is a non-randomized, parallel assignment of approximately 40 patients, which will evaluate the primary outcome of overall response rate with secondary outcomes of progression-free survival.

Conclusions

Aggressive natural killer-cell leukemia remains a rare, yet devastating disease that does not respond to typical chemoradiation regimens. The continued adaptation of treatment regimens has led to the discovery of multiple techniques that allow for appropriate responses with limited toxicity. Regimens that provide lower dose intensity of chemoradiation with subsequent allogeneic stem cell transplantation have shown some benefits. While progression-free survival rates have had considerable improvement over the past several years, relapse remains an issue. Novel molecular therapeutic targets have shown some promise in vitro by targeting common proteins involved in apoptosis and epigenetic cell silencing. Further clinical trials that utilize these chemoradiation techniques along with transplantation, personalized molecular targeting, and prophylaxis for CNS relapse may achieve the greatest success with these patients.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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