NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Hodgkin’s Lymphomas

Version 2.2015

NCCN.org

Continue
Adult T-Cell Leukemia/Lymphoma
**DIAGNOSIS**

**ESSENTIAL:**
- HTLV-1 serology: ELISA and confirmatory western blot if ELISA is positive. If western blot is indeterminate, then HTLV-1 PCR can be performed.
- CBC and peripheral blood smear for atypical cells: lymphocytosis (ALC >4000/μL in adults) in acute and chronic subtypes
- Flow cytometry on peripheral blood

**USEFUL IN CERTAIN CIRCUMSTANCES:**
- Biopsy of lymph nodes (excisional), skin biopsy, GI tract, or bone marrow biopsy is required if:
  - Diagnosis is not established on peripheral blood, or
  - Ruling out an underlying infection (tuberculosis, histoplasmosis, toxoplasmosis, etc.)
- If biopsy performed, the recommended panel for paraffin section immunohistochemistry:
  - CD3, CD4, CD5, CD7, CD8, CD25, CD30

**WORKUP**

**ESSENTIAL:**
- Complete H&P examination, including complete skin exam
- Electrolytes, BUN, creatinine, serum calcium, serum LDH
- Chest/abdominal/pelvic/neck CT scan
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

**USEFUL IN SELECTED CASES:**
- Upper gastrointestinal endoscopy
- Skeletal survey in symptomatic patients
- Stool examination for parasites (strongyloides is most likely)
- PET-CT scan
- Central nervous system evaluation: CT scan, MRI and/or lumbar puncture in all patients with acute or lymphoma subtypes or in patients with neurologic manifestations

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Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**ATLL SUBTYPE**

<table>
<thead>
<tr>
<th>Chronic/Smoldering</th>
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</table>

**FIRST-LINE THERAPY**

- Clinical trial
- Observation
- Skin-directed therapies as clinically indicated *(See Mycosis Fungoides/Sezary Syndrome [MFSS-A]*)
- Zidovudine and interferon

**INITIAL RESPONSE (at 2 mo)**

- Responders
  - Continue treatment with zidovudine and interferon
  - Clinical trial
  - Chemotherapy *(See Suggested Treatment Regimens [ATLL-B]*)
  - Best supportive care
- Non-responders

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†Supportive care: anti-infectious prophylaxis with sulfamethoxazole/trimethoprim + strongyloidosis is recommended.

‡Outside of a clinical trial, if a patient is not responding or is progressing, treatment with zidovudine and interferon should be stopped. If there is evidence of clinical benefit, treatment should continue until best response is achieved. If life-threatening manifestations, treatment can be discontinued before the 2-month period.

See references for zidovudine and interferon (ATLL-C).

See Response Criteria for ATLL (ATLL-A). Responders include CR, uncertified PR, and PR.
**ATLL SUBTYPE**

<table>
<thead>
<tr>
<th>Acute</th>
<th>Lymphoma</th>
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**FIRST-LINE THERAPY**

- Clinical trial or Zidovudine and interferon or Chemotherapy (See Suggested Treatment Regimens [ATLL-B])

**INITIAL RESPONSE (after 2 cycles)**

- **Responders**
  - Continue prior therapy or Consider allogeneic stem cell transplant
  - Clinical trial or Best supportive care or Alternate therapy not previously treated with:
    - See [ATLL-B](#) or [See TCEL-B for Second-line therapy](#)
    - Zidovudine and interferon

- **Non-responders**
  - Continue chemotherapy or Consider allogeneic stem cell transplant
  - Clinical trial or Best supportive care or Chemotherapy (See [TCEL-B for Second-line therapy](#))

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**References:**

- Supportive care: anti-infectious prophylaxis with sulfamethoxazole/trimethoprim + strongyloidosis is recommended.
- Outside of a clinical trial, if a patient is not responding or is progressing, treatment with zidovudine and interferon should be stopped. If there is evidence of clinical benefit, treatment should continue until best response is achieved. If life-threatening manifestations, treatment can be discontinued before the 2-month period.
- Antiviral therapy is not effective.
- CNS prophylaxis: intrathecal chemotherapy is recommended (methotrexate and cytarabine and corticosteroids).
# RESPONSE CRITERIA FOR ATLL\(^a\)

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Lymph Nodes</th>
<th>Extranodal Masses</th>
<th>Spleen, Liver</th>
<th>Skin</th>
<th>Peripheral Blood</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission*</td>
<td>Disappearance of all disease</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal(^†)</td>
<td>Normal</td>
</tr>
<tr>
<td>Uncertified complete remission*</td>
<td>Stable residual mass in bulky lesion</td>
<td>≥75% decrease(^‡)</td>
<td>≥75% decrease(^‡)</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal(^†)</td>
<td>Normal</td>
</tr>
<tr>
<td>Partial remission*</td>
<td>Regression of disease</td>
<td>≥50% decrease(^‡)</td>
<td>≥50% decrease(^‡)</td>
<td>No increase</td>
<td>≥50% decrease</td>
<td>≥50% decrease</td>
<td>Irrelevant</td>
</tr>
<tr>
<td>Stable disease*</td>
<td>Failure to attain complete/partial remission and no progressive disease</td>
<td>No change in size</td>
<td>No change in size</td>
<td>No change in size</td>
<td>No change in size</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Relapsed disease or progressive disease</td>
<td>New or increased lesions</td>
<td>New or ≥50% increase(^§)</td>
<td>New or ≥50% increase(^§)</td>
<td>New or ≥50% increase</td>
<td>≥50% increase</td>
<td>New or ≥50% increase(^#)</td>
<td>Reappearance</td>
</tr>
</tbody>
</table>

*Required that each criterion be present for a period of at least 4 weeks.
\(^†\)Provided that <5% of flower cells remain, complete remission is judged to have been attained if the absolute lymphocyte count, including flower cells, is <4 x 10⁹/L.
\(^‡\)Calculated by the sum of the products of the greatest diameters of measurable disease.

\(^§\)Defined by ≥50% increase from nadir in the sum of the products of measurable disease.

\(^#\)Defined by ≥50% increase from nadir in the count of flower cells and an absolute lymphocyte count, including flower cells, of >4 x10⁹/L.


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SUGGESTED TREATMENT REGIMENS
(in alphabetical order)

- Chemotherapy\(^a\)
  - CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)
  - CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone)
  - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine

\(^a\)There are no published data regarding the use of these regimens; however, they are used at NCCN Member Institutions for the treatment of ATLL.
REFERENCES FOR ZIDOVUDINE AND INTERFERON

**Zidovudine and interferon**


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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Adult T-cell Leukemia/Lymphoma

Adult T-cell leukemia/lymphoma (ATLL) is a type of peripheral T-cell malignancy caused by a retrovirus, the human T-cell lymphotropic virus type I (HTLV-1), and is associated with a long period of latency (often manifesting several decades after exposure). ATLL is endemic to several regions, including southwest regions in Japan, the Caribbean, and parts of central Africa, owing to the distribution of HTLV-1. ATLL comprised about 10% of the diagnosis for confirmed cases of PTCL or NK/T-cell lymphomas (N=1,153). ATLL was rare in North America or Europe (≤2%), but prevalent in Asia (25%), with all cases from Asia originating in Japan. Among HTLV-1 carriers in Japan, the cumulative life-time risk of developing ATLL is estimated to be 2.5%; the annual incidence of ATLL in Japan is approximately 700.

ATLL can be associated with an aggressive disease course, with median overall survival (OS) of 6 to 10 months among patients with the acute or lymphoma subtypes. The Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG) have classified ATLL into four subtypes (smoldering, chronic, acute, or lymphoma) based on laboratory evaluations (e.g., serum lactate dehydrogenase [LDH], calcemia, lymphocytosis) and clinical features of ATLL (e.g., lymphadenopathy, hepatosplenomegaly, skin involvement). The smoldering and chronic subtypes are considered indolent forms of ATLL. Both subtypes are usually characterized by 5% or more abnormal T-lymphocytes in the peripheral blood and may have skin or pulmonary lesions (but no ascites or pleural effusion). In addition, the smoldering subtype is associated with a normal lymphocyte count, normal serum calcium level, LDH levels within 1.5 times upper normal limit, and no involvement of liver, spleen, CNS, bone, or gastrointestinal (GI) tract. The expected median OS for this subtype generally exceeds 5 years.

The chronic subtype is characterized by absolute lymphocytosis (≥4 x 10^9/L) with T-lymphocytes ≥3.5 x 10^9/L, normal calcium level, LDH levels within 2 times upper normal limit, and no involvement of CNS, bone or GI tract; lymphadenopathy and involvement of liver and spleen may be present. The lymphoma subtype is characterized by absence of lymphocytosis, ≤1% abnormal T-lymphocytes, and histologically-proven lymphadenopathy with or without extranodal lesions. The acute subtype usually presents with leukemic manifestation and tumour lesions, and represent cases that are not classified as any of the other 3 subtypes above. The acute subtype is associated with a rapidly progressive disease course, and features including elevated LDH levels, hypercalcemia (with or without lytic bone lesions), B symptoms, generalized lymphadenopathy, splenomegaly, hepatomegaly, skin involvement, and organ infiltration.

The smoldering and chronic subtypes have a more favorable prognosis compared with the acute or the lymphoma subtypes. In the analysis of patients with ATLL (N=818; mean age 57 years) from the Lymphoma Study Group of JCOG, the estimated 4-year OS rates for patients with acute, lymphoma, chronic, and smoldering subtypes were 5%, 6%, 27%, and 63%, respectively. The median OS was 6, 10, 24 months, and not yet reached, respectively. The maximum duration of follow-up was 7 years in this study. The analysis from the International PTCL Project confirmed the poor outcomes of patients with acute or lymphoma subtypes of ATLL, with a median OS of 10 months. In a recent report from a long-term follow-up of patients with newly diagnosed indolent ATLL (N=90), the median OS was 4 years and the estimated 5-, 10-, and 15-year survival rates were 47%, 25%, and 14%, respectively. In the subgroup analysis, the 15-year OS rate and median OS tended to be higher for the chronic subtype (15% and 5 years, respectively) than the smoldering subtype (13% and 3 years).
respectively). These long-term outcomes appear poorer than expected for patients with indolent ATLL; the heterogeneity in outcomes among patients with even the indolent subtype of the disease may be explained, in part, by differences in patient- and disease-related factors.

In patients with ATLL, poor performance status, elevated LDH level, ≥4 total involved lesions, hypercalcemia and age ≥40 years have been identified as major adverse prognostic factors based on data from a large number of patients. Among patients with the chronic subtype, factors such as poor performance status, ≥4 total involved lesions, bone marrow involvement, elevated LDH, elevated blood urea nitrogen, and low albumin levels have been identified as potential prognostic factors for decreased survival. Further studies with a larger number of patients are needed to elucidate prognostic factors that may help to further risk stratify patients with indolent ATLL. For patients with aggressive subtypes of ATLL, the International PTCL Project recently reported that the International Prognostic Index (IPI) was a useful model for predicting outcomes. Based on univariate analysis, presence of B symptoms, platelet count <150 × 10^9/L, and high IPI score (≥3) were found to be associated with decreased OS. Based on multivariate analysis, however, IPI score was the only independent predictor for OS outcomes. Recently, a report based on data from patients with ATLL in North America (N=89; acute or lymphoma subtypes in 79%) found that IPI scores were not always predictive for ATLL outcomes, and proposed a new prognostic model. In this study, the investigators identified 3 prognostic categories based on the following factors: ECOG performance status, Ann Arbor stage, age, and serum calcium level at diagnosis.

In the NCCN Guidelines, patients with ATLL are classified into 4 subtypes (chronic, smoldering, acute and lymphoma) according to the Shimoyama criteria.

**Diagnosis**

The diagnosis of ATLL requires histopathology and immunophenotyping of tumor lesion, peripheral blood smear analysis for atypical cells, flow cytometry on peripheral blood and HTLV-1 serology. The presence of ≥5% T-lymphocytes with an abnormal immunophenotype in the peripheral blood is required for the diagnosis of ATLL in patients without histologically proven tumor lesions. The cytological features of ATLL may be broad, but typical ATLL cells are characterized by so-called ‘flower cells’, which show distinct polynuclear nuclei with homogeneous and condensed chromatin, small or absent nucleoli, and agranular and basophilic cytoplasm. These cytological characteristics are most evident in the acute subtype of the disease. HTLV-1 serology should be assessed by ELISA, and if positive, a confirmed by western blot. If the result from western blot is indeterminate, then PCR analysis for HTLV-1 can be performed. Monoclonal integration of HTLV-1 proviral DNA occurs in all cases of ATLL; HTLV-1 integration patterns have been reported to have clinical and prognostic implications for ATLL.

Bone marrow biopsy or aspiration is generally not required to establish the diagnosis of ATLL. However, bone marrow evaluation may be useful as bone marrow involvement has been reported as an independent predictor of poor prognosis in ATLL. If the diagnosis of ATLL is not established on peripheral blood examination, bone marrow biopsy or biopsy of the lymph nodes or lesions in skin or GI tract should be performed. Biopsy of the suspicious lesion may also help to rule out certain underlying infections (e.g., tuberculosis, histoplasmosis, and toxoplasmosis). Excisional biopsy is recommended instead of core needle biopsy for the lymph nodes.

If a biopsy is performed, the immunophenotyping panel should at minimum include the following markers: CD3, CD4, CD7, CD8, and CD25. The typical immunophenotype in most patients with ATLL
involves mature CD4-positive T cells with expression of CD2, CD5, CD25, CD45RO, CD29, T-cell receptor αβ and HLA-DR. Most ATLL cells lack CD7 and CD26 and have a dim CD3 expression. In the Guidelines, the following is included as representative of a typical immunophenotype for ATLL: CD2+, CD3+, CD4+, CD7-, CD8-, CD25+, CD30-/+, TCR αβ+.

The clinical features of ATLL differ by subtype and disease stage, but patients with the most common acute or lymphoma subtypes may frequently present with lymphadenopathy (77%), fatigue (32%), anorexia (26%), skin eruptions (23%), abdominal pain (23%), pulmonary complications (18%; due to leukemic infiltration and/or infections), splenomegaly (13%), and hepatomegaly (10%). Bone marrow involvement (28%) and CNS involvement (10%) are also not uncommon.

**Workup**

The initial workup for ATLL should include a comprehensive physical examination with complete skin examination, and CT scans of the chest, abdomen and pelvis. Most patients with acute ATLL have elevated LDH levels, and lymphocytosis is found in patients with the acute or chronic type at presentation. Laboratory evaluations should include a complete blood count (CBC) and metabolic panel (serum electrolyte levels, calcium, creatinine and blood urea nitrogen), and measurement of serum LDH levels.

Upper GI tract endoscopy should be considered in selected cases since GI tract involvement is frequently observed in patients with aggressive ATLL. CNS evaluation using CT scan, MRI and/or lumbar puncture may also be useful for all patients with acute or lymphoma subtypes or in patients with neurological manifestations.

**Response Criteria**

The current response criteria used for ATLL are based on modifications to the original 1991 JCOG response criteria as suggested at the international consensus meeting. The modified response criteria reflect the widely used criteria for CLL and NHL, which were published in 1996 and 1999, respectively. These response criteria are based on the normalization or reduction in the size of enlarged lymph nodes and extranodal masses (as calculated by the sum of the products of the greatest diameters of measurable disease), reduction in the size of spleen or liver and decrease in the involvement of peripheral blood, bone marrow and skin. The response is categorized as a complete remission (CR; defined as complete disappearance of all clinical, microscopic, and radiographic evidence of disease and absolute lymphocyte count, including flower cells, <4 x 10^9/L in the peripheral blood), partial remission (PR; defined as ≥50% reduction in the sum of the products of the greatest diameters of measurable disease without the appearance of new lesions, no increase in spleen or liver size, ≥50% reduction in skin involvement, and ≥50% reduction in absolute lymphocyte counts in peripheral blood), stable disease (SD; failure to achieve CR or PR with no progressive disease) and relapsed disease or progressive disease (PD; new or ≥50% increase in lymph node lesions, extranodal mass, or splenomegaly/hepatomegaly, ≥50% increase in skin involvement, 50% increase from nadir in the count of flower cells and an increase in absolute lymphocyte count, including flower cells, of >4 x 10^9/L). Each of the criterion for the response categories should be observed for a minimal period of 4 weeks to qualify for the response (e.g., CR, PR, SD). The response criteria also includes a category for unconfirmed CR, defined as ≥75% reduction in tumor size but with a residual mass after treatment, with an absolute lymphocyte count, including flower cells, of <4 x 10^9/L. The usefulness of PET or PET-CT...
has not been evaluated in the response assessment of patients with ATLL.

**Treatment Options**

The ATLL subtype is an important factor for predicting prognosis and deciding appropriate treatment strategies. Smoldering and chronic subtypes are considered indolent, and are usually managed similarly to indolent NHL with watchful waiting until symptomatic disease. In contrast, the acute and lymphoma subtypes typically require immediate therapy.

A number of small studies and cases have reported on the activity of the combination of an anti-retroviral agent zidovudine and interferon (IFN)-alfa in patients with ATLL. Among patients with primarily treatment-naïve aggressive ATLL, antiviral therapy with zidovudine and IFN-alfa resulted in overall response rate (ORR) of 58%-80% and CR rates of 20%-50%. Outcomes with this therapy for previously treated patients with relapsed/refractory disease were poorer, with ORR 17%-67% (nearly all PRs). The results of a meta-analysis on the use of zidovudine and IFN for patients with ATLL were recently reported by Bazarbachi et al (N=254). Most of the patients (n=207 evaluable) in this analysis had the acute (47%) or lymphoma (41%) subtypes, with the remaining patients presenting with indolent disease. Patients had been treated with first-line antiviral therapy alone (n=75; comprising a combination of zidovudine and IFN-alfa in 97% of cases), chemotherapy alone (n=77; CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] in 86% of cases) or chemotherapy followed by maintenance antiviral therapy (n=55). Among the patients who received first-line antiviral therapy alone, 60% had the acute subtype; in contrast, among the patients who received chemotherapy alone, 62% had the lymphoma subtype. In patients with available survival data and recorded first-line therapy (n=207), the 5-year OS rates were 46%, 20% and 12%, respectively, for patients who received first-line antiviral therapy alone, chemotherapy alone and chemotherapy followed by antiviral therapy. The ORR was 66% (CR in 35%) among patients who received first-line antiviral therapy (n=62 evaluable) and 88% (CR in 25%) among those who received first-line chemotherapy alone (n=48 evaluable). Among patients who received chemotherapy followed by antiviral therapy (n=14 evaluable), the ORR was 93% (CR in 50%). For all patients with follow-up survival data (n=238), the median OS was 12 months and the 5-year OS rate was 23%. In the subgroup analysis by ATLL subtype, median OS was 6 months, 13 months, and not reached, respectively, in patients with acute, lymphoma and indolent (chronic or smoldering) subtypes, the 5-year OS rate was 15%, 16%, and 76%, respectively. In the subgroup analysis by first-line treatment regimen, antiviral therapy resulted in significantly longer median OS (17 months vs. 12 months) and higher 5-year OS rate (46% vs. 14%) compared with chemotherapy (with or without maintenance antiviral therapy). Interestingly, only the patients with the acute and indolent subtype benefited significantly from first-line antiviral therapy, whereas patients with the lymphoma subtype had worse survival with antiviral therapy and better outcomes with first-line chemotherapy (with or without maintenance antiviral treatment). Multivariate analysis showed that only the ATLL subtype and type of first-line treatment were significant independent predictors for poorer OS. These data suggest that antiviral therapy with zidovudine and IFN-alfa is effective in patients with leukemic ATLL, but not in the lymphoma subtype. A recent retrospective analysis evaluated outcomes in patients with aggressive ATLL (N=73; 60% had lymphoma subtype) treated with chemotherapy alone (n=39; primarily with CHOP-containing regimens) or combined therapy with chemotherapy and antiviral agents (zidovudine and INF-alfa; given concurrent or sequential to chemotherapy or deferred).
median OS among patients with the acute and lymphoma subtypes was 7.5 months and 10 months, respectively. The use of antiviral treatments (at any point on the study) was associated with significant OS benefit for both the subgroups with acute and lymphoma ATLL. Among patients with the lymphoma subtype (n=32), treatment with first-line combination therapy (with chemotherapy and antiviral agents) or chemotherapy with deferred antivirals resulted in significant OS benefits compared with chemotherapy alone.

In patients with ATLL, combination chemotherapy with CHOP has resulted in ORR of 64% to 88% and CR rates of 18% to 25%. Median OS in published reports ranges from about 8 to 12 months. In the aforementioned meta-analysis of data from patients with ATLL treated with first-line therapies, chemotherapy (primarily CHOP) alone resulted in median OS of 10 months and chemotherapy with or without maintenance antiviral therapy resulted in median OS of 12 months. As alluded to earlier in the discussion, patients with the lymphoma subtype appeared to benefit more from first-line therapy with CHOP or CHOP-like chemotherapy (with or without maintenance antivirals) than with antivirals alone. In the subgroup of patients with the lymphoma subtype, OS outcome was significantly improved with first-line chemotherapy (n=72; median OS 16 months; 5-year OS 18%) compared with first-line antiviral treatment alone (n=13; median OS 7 months; 5-year OS 0%; P=0.009). Several prospective studies have evaluated the role of more intensive chemotherapy combination regimens. A phase II multicenter study investigated the activity of CHOP followed by a regimen with etoposide, vindesine, ranimustine, mitoxantrone, and G-CSF in patients with ATLL (N=81). The ORR with this intensive regimen was 74% (CR in 36%) and the median duration of response was 8 months. The median OS for all patients remained rather short, at 8.5 months; the 3-year OS rate was 13.5%. In a small phase II trial conducted by the AIDS Malignancy Consortium in patients with aggressive ATLL (N=19), EPOCH chemotherapy followed by antiretroviral therapy (zidovudine, lamivudine, IFN-alfa up to 1 year) resulted in an ORR of 58% (CR in 10.5%) and a median duration of response of 13 months. Although this regimen appeared to be active in this patient population, viral reactivation during therapy coincided with disease progression, which likely contributed to treatment failure. A phase II trial by JCOG evaluated an intensive multidrug combination chemotherapy regimen comprising VCAP-AMP-VECP [vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP), doxorubicin, ranimustine, and prednisone (AMP), and vindesine, etoposide, carboplatin, and prednisone (VECP)], supported by G-CSF, in patients with aggressive ATLL (N=93). The ORR with this regimen was 81% with a CR in 35.5% of patients. The median OS was 13 months and the estimated 2-year OS rate was 31%. Grade 4 neutropenia (65%) and thrombocytopenia (53%) were frequently observed despite the use of G-CSF. Based on the promising results seen in this study, a randomized phase III trial was conducted by JCOG to evaluate first-line therapy with VCAP-AMP-VECP compared with biweekly CHOP (CHOP-14) in patients with aggressive ATLL (N=118). The CR rate was significantly higher with VCAP-AMP-VECP compared with CHOP-14 (40% vs. 25%; P=0.02) but the 1-year PFS rate (28% vs. 16%) and 3-year OS rate (24% vs. 13%) were not significantly different. Median PFS (7 months vs. 5 months, respectively) and median OS (13 months vs. 11 months, respectively) were not different between treatment arms. VCAP-AMP-VECP regimen was associated with higher incidence of toxicities compared with CHOP-14, including grade 4 neutropenia (98% vs. 83%), grade 4 thrombocytopenia (74% vs. 17%) and grade 3-4 infections (32% vs. 15%). Recently, a very limited number of ATLL cases have been treated with hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and
dexamethasone), a regimen more commonly used in the treatment of patients with aggressive B-cell NHL and adult acute lymphoblastic leukemias.\(^{31}\) Promising outcomes in terms of durable CRs have been reported with this regimen in two cases of ATLL\(^{31}\); however, prospective evaluations are needed.

Allogeneic HSCT (using myeloablative or non-myeloablative conditioning) may improve outcomes for some patients with ATLL\(^{32-37}\) with suggestion of a graft-versus-leukemia effect.\(^{33,35}\) Studies with allogeneic HSCT (primarily using myeloablative conditioning) have reported promising disease-free and OS outcomes in patients with ATLL, with median leukemia-free survival exceeding 17 months and 3-year OS rate of about 45%.\(^{33,35,37}\) However, the transplant procedure was associated with a high treatment-related mortality (TRM) rate of 40% to 63%.\(^{33,35,37}\) In a multicenter retrospective analysis that evaluated outcomes in patients with aggressive ATLL who received myeloablative allogeneic HSCT (N=40), the median OS for all patients following transplant was about 10 months.\(^{33}\) Acute graft-versus-host disease (GvHD) developed in 67% of patients. The estimated 3-year relapse-free survival and OS rate was 34% and 45%, respectively. The incidence of TRM was 42.5%, with early TRM (within 6 months of transplant) occurring in 13 patients (32.5%).\(^{33}\) A large retrospective analysis was conducted in patients with ATLL who underwent allogeneic HSCT (related or unrelated) (N=386).\(^{34}\) After a median follow up of 41 months, the 3-year OS rate for this patient cohort was 33%. Overall, the incidence of TRM was 43%, which was mainly due to infectious complications and organ failure. Based on multivariate analysis, patient age (>50 years), male sex, lack of a CR at the time of transplant, and the use of unrelated or cord blood were identified as adverse prognostic factors for OS outcomes.\(^{34}\) In an effort to reduce the high rate of TRM observed with allogeneic HSCT, small prospective studies have been conducted to evaluate the use of reduce-intensity conditioning (RIC) in allogeneic HSCT for patients with ATLL.\(^{32,36}\) In a combined analysis from two clinical trials (N=29), the 5-year OS rate with RIC allogeneic HSCT was 34%.\(^{32}\) The NRM rate was 27.5%; 11 patients died due to disease progression. Ten patients are alive at a median follow up of 82 months following transplant.\(^{32}\)

A recent retrospective study evaluated the role of myeloablative conditioning and RIC allogeneic HSCT in a large group of patients with ATLL in Japan (N=586).\(^{40}\) The majority of patients had either acute (57%) or lymphoma (28%) subtypes. Patients who received RIC for HSCT were older than those who received myeloablative conditioning regimens (median age 57 years vs. 49 years). The median OS (survival measured from time of HSCT) was 9.5 months among patients who received myeloablative conditioning, with a 3-year OS of 39%. For patients who received RIC, the median OS was 10 months, with a 3-year OS of 34%. The 3-year cumulative incidence of TRM was 38% with myeloablative conditioning and 33% with RIC. The 3-year cumulative incidence of ATLL-related death was 22.5% and 33%, respectively.\(^{40}\) Based on multivariate analysis, older age (>55 years), male sex, lack of CR at time of HSCT, poorer performance status (PS ≥1), and unrelated donor HSCT were significant independent factors associated with decreased OS outcomes. Older age (>55 years) was a significant independent factor for poorer OS among patients who received myeloablative conditioning, but not for those who received RIC. In multivariate analysis, significant independent factors for risk of TRM included male sex, poorer performance status (PS ≥1), and unrelated donor HSCT; significant independent factors influencing risks for ATLL-related death included non-CR at time of HSCT, poor PS (PS ≥2), and RIC.\(^{40}\) This analysis suggested that use of
myeloablative conditioning or RIC resulted in similar outcomes with allogeneic HSCT, and that HSCT may offer long-term survival in some patients with ATLL. Prospective studies in larger groups of patients are warranted to further evaluate the role of allogeneic HSCT (with myeloablative conditioning or RIC) in the management of ATLL.

Patients with ATLL who relapse after allogeneic HSCT have poor prognosis and very limited treatment options. In a retrospective analysis of patients who progressed or relapsed after first allogeneic HSCT (N=35), donor lymphocyte infusion (DLI) was reported to induce long-term remissions in a few patients. Most patients in this analysis received withdrawal of immunosuppression as the initial intervention. Among the patients who subsequently received DLI (n=9), the median OS after relapsed/progression was 17 months; the 3-year OS was 33%. Debulking of tumors (with dose-reduced CHOP or RT) prior to DLI seemed to be associated with improved outcomes; response was achieved in 5 of 6 patients who underwent pre-DLI cytoreductive therapy. DLI resulted in remission lasting more than 3 years in 3 of the patients. Among the patients who did not receive DLI (n=26), the median OS was 4 months and the 3-year OS was 14%. The majority of these patients were treated with chemotherapy regimens following initial withdrawal of immunosuppression. This analysis showed that induction of graft-versus-ATLL effect via treatments such as DLI may provide long-lasting remission in select patients with relapsed ATLL. However, prospective clinical trials are needed to confirm these findings.

**NCCN Recommendations**

There are no optimal standard treatment regimens for the management of ATLL. Thus, the NCCN Guidelines panel recommends enrollment in clinical trials as one of the options for all patients with ATLL. Prophylaxis with anti-*Strongyloides* agents and prophylaxis with sulfamethoxazole-trimethoprim to prevent *Pneumocystis jirovecii* pneumonia are recommended for all patients undergoing treatment for ATLL.10

**Primary Therapy**

For patients with chronic or smoldering ATLL subtypes, observation is a valid option for asymptomatic cases since both of these subtypes are considered indolent diseases. Alternatively, if symptoms are present, these patients can be managed with skin-directed therapies (as recommend for patients with mycosis fungoides or Sézary syndrome within this NCCN Guidelines for NHL) for skin lesions, as appropriate, or with antiviral therapy with combination of zidovudine and IFN-alfa. As previously discussed, enrollment in suitable clinical trials is encouraged, where available.

For patients with acute ATLL, treatment options include participation in clinical trials, antiviral therapy with zidovudine and IFN-alfa, or combination chemotherapy regimens (i.e., CHOP, CHOEP, dose-adjusted EPOCH, or hyper-CVAD; all based on limited data only). For patients with the lymphoma subtype, primary treatment options include participation in clinical trials or combination chemotherapy (as mentioned above for acute ATLL); antiviral therapy alone is not considered effective for this group of patients.23 CNS prophylaxis (with intrathecal methotrexate and cytarabine and corticosteroids) is recommended in patients with lymphoma subtype. No optimal treatment has been defined for these patients with aggressive ATLL and efficacy of long-term treatment is limited. As discussed earlier, allogeneic HSCT may be beneficial in some patients with ATLL.
stopped. If there is evidence of clinical benefit, treatment should continue until best response is achieved. The duration of initial therapy is usually 2 months. If life threatening manifestations occur, however, treatment can be discontinued before this period.

The optimal chemotherapy regimen for patients with ATLL is not yet established. The regimens listed in the NCCN Guidelines are based on institutional preferences and include CHOP, CHOEP, dose-adjusted EPOCH or hyper-CVAD.

Mogamulizumab (KW-0761) is a humanized monoclonal antibody approved for the treatment of patients with relapsed or refractory CCR4-positive ATLL in Japan. The approval was based on results of a multicenter phase II study for patients with relapsed, aggressive CCR4-positive ATLL (N=28). The primary endpoint of the trial was ORR; the secondary endpoints included PFS and OS outcomes. Patients were treated with mogamulizumab IV 1 mg/kg once per week for 8 weeks, which was the dose derived from the phase I study. The ORR among evaluable patients (n=26) was 50% (95% CI, 30–70%). The median PFS and OS were approximately 5 months and 14 months, respectively. The most common adverse events included infusion reactions (89%) and skin rashes (63%). Mogamulizumab is an investigational agent in the U.S. and has not been approved for any indication by the FDA. This agent is currently being evaluated in previously treated patients with ATLL in a multicenter open-label randomized study in the U.S. and elsewhere.

Response Assessment and Additional Therapy
For patients with chronic or smoldering ATLL who achieve an initial response (at 2 months following start of treatment; responders include those with a CR, uncertified PR, or PR), continuation of zidovudine and IFN-alfa is recommended. If the patient presents with persistent disease or has disease progression at 2 months from start of treatment (non-responders to initial therapy), options for additional therapy include participation in clinical trials, where available, or combination chemotherapy regimens (i.e., CHOP, EPOCH, or hyper-CVAD) or best supportive care. Allogeneic HSCT should be considered for patients with acute or lymphoma subtype.

For patients with acute or lymphoma ATLL subtypes who achieve an initial response to primary therapy, continuation of the prior therapy or allogeneic HSCT (if donor is available) are appropriate options. Patients with acute ATLL with persistent or progressive disease following primary therapy (non-responders) should be treated in the context of a clinical trial, where possible, best supportive care or an alternate regimen not previously used (under first-line therapy for ATLL, for second-line therapy recommended in the Guidelines for PTCL, or antiviral therapy with zidovudine and IFN). In non-responding patients with lymphoma ATLL subtypes after first-line therapy, options for second-line therapy include treatment in the context of a clinical trial, best supportive care or second-line therapy options based on the recommendations for PTCL. In patients with acute or lymphoma ATLL subtypes who achieve a response to second-therapy, allogeneic HSCT should be considered if a donor is available.
References


