ATLL

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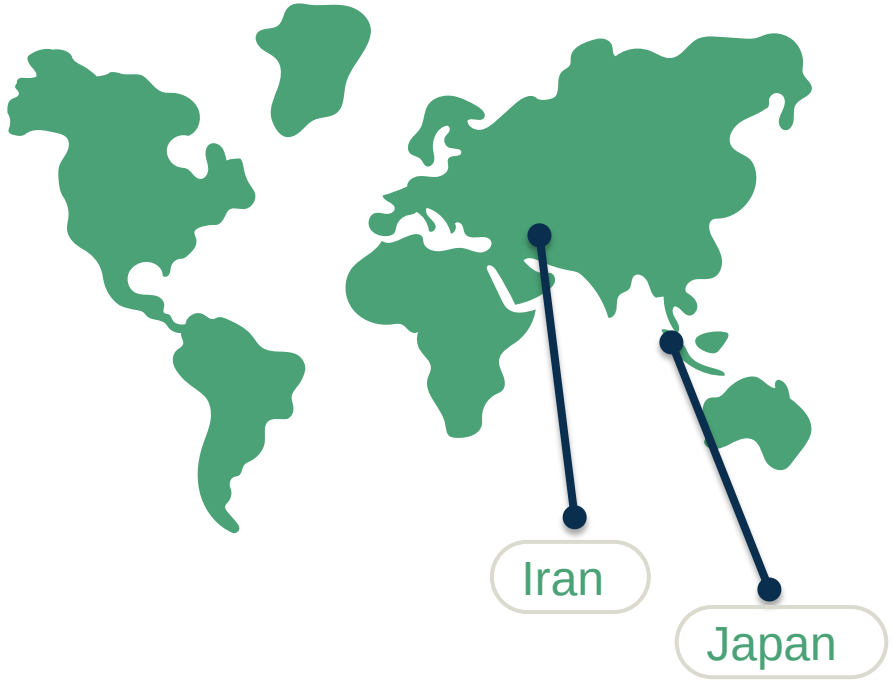
INTRODUCTION

Adult T cell leukemia-lymphoma (ATL) is a mature T cell malignancy that generally presents with widespread involvement of **lymph nodes**, **peripheral blood**, and/or skin.

Although ATL is often highly aggressive, the clinical presentation is variable and, in some cases, it is an indolent disorder. ATL is caused by chronic infection with the human T-lymphotropic virus, type I (HTLV-I).

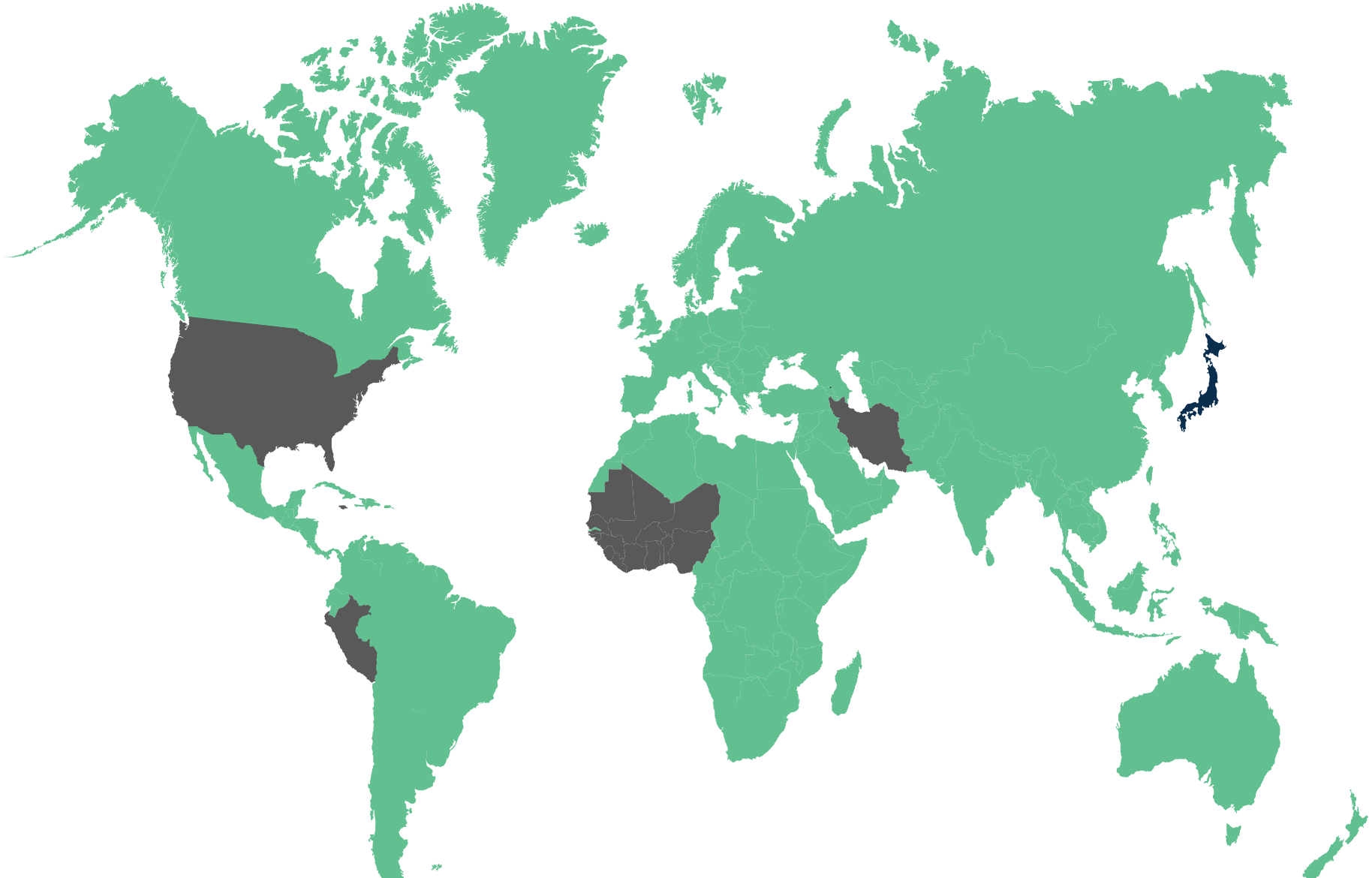
EPIDEMIOLOGY

- ATL is an uncommon lymphoid neoplasm that occurs in patients with human T-lymphotropic virus, type I (HTLV-I) infection.
- Infection with HTLV-1 is endemic in:
  - Several islands in southwestern Japan
  - The Caribbean basin (eg, Jamaica and Trinidad)
  - Western Africa
  - Peru
  - North-East Iran
  - The southeastern portion of the United States



most affected patients live in or originate from these areas.

- HTLV-I infects an estimated 5 to 10 million people worldwide
- In the United States as a whole, the incidence of ATL is approximately 0.05 cases per 100,000 people
- In non-endemic areas, such as the United States and Europe, have prevalence rates of less than 1 percent



- The median age at diagnosis is in the sixth decade.
- However, median age at diagnosis can vary with geographic location.
- As an example, a study of 126 patients with ATL from Jamaica reported a median age of 43 years.

TRANSMISSION

I. Mother to child transmission
II. Sexual transmission
III. Injection drug use
IV. Occupational exposure
V. Zoonotic transmission
VI. Tissue donation

ANTIVIRAL TREATMENT & PREVENTION

- Treatment is not indicated for asymptomatic individuals, and management of such patients is confined to the early diagnosis of clinical manifestations and to the prevention of transmission to others.
- The latter includes avoidance of breastfeeding in endemic areas, screening of blood donors, as well as the promotion of safe sex and discouraging needle sharing

PATHOGENESIS

ATL is uniformly associated with human T-lymphotropic virus type I (HTLV-I) infection of CD4-positive T cells, the cell of origin for the tumor

It is estimated that there are

5-10 million

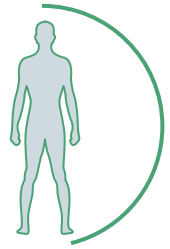
HTLV-1 carriers worldwide.

PATHOGENESIS

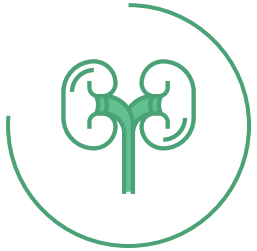
The long-term risk of developing ATL following infection with HTLV-I in endemic areas has been estimated to be 4 to 5 percent, usually after a latency period of several decades.

Exposure to the virus early in life increases the risk of eventual development of ATL.

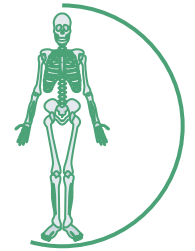
CLINICAL FEATURES



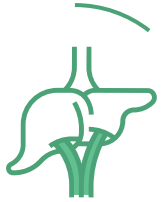
Generalized lymphadenopathy



Hypercalcemia



Lytic bone lesions
&
skin lesions



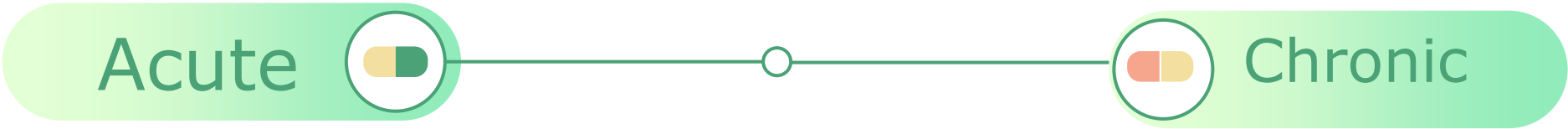
Hepatosplenomegaly

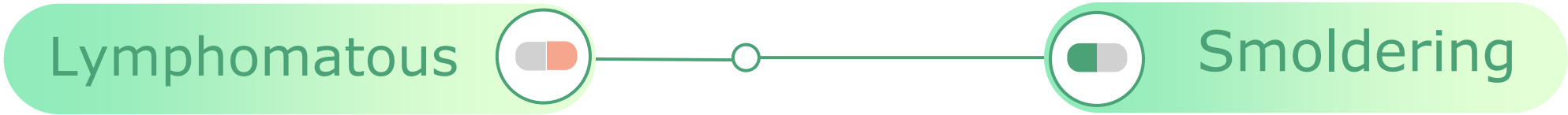
immunosuppression

The frequency of these differs among patient groups and has been the basis on which clinical variants have been defined.

Clinical variants

Several clinical variants of ATL have been described





these appear to have differing genomic alterations and different clinical courses

Clinical variants

Acute

- The most common presentation of ATL, occurring in about 60 percent of cases, is the acute variant, which has a generally poor prognosis with survival measured in months to a year despite aggressive treatment.
- Patients with the acute variant of ATL most frequently present with systemic symptoms:
  - Organomegaly
  - Lymphadenopathy
  - An elevated lactate dehydrogenase (LDH) level
  - Circulating malignant cells
  - The white blood cell (WBC) count is usually elevated and may be higher than 100,000/microL

Clinical variants

Acute

- Common presenting signs or symptoms include:
  - A high peripheral blood white blood cell count is common due to the presence of circulating lymphocytes with highly abnormal convoluted nuclei.
  - Bone marrow involvement is observed in 5 to 35 percent of cases.
  - Lymphadenopathy is seen in almost all cases.
  - Involvement of the liver and spleen is present in approximately 16 and 22 percent, respectively.
  - 40 to 50 percent will have hypercalcemia with or without lytic bone lesions at presentation and an additional third will develop hypercalcemia at some point during the course of their disease

Clinical variants

Acute

- Common presenting signs or symptoms include:
  - Approximately 25 percent will have skin lesions at diagnosis, often simulating those seen in mycosis fungoides.
  - Skin lesions may be:
    - patches (7 percent)
    - plaques (27 percent)
    - papules (19 percent)
    - tumors (39 percent)
    - erythrodermic lesions (4 percent)
    - purpuric lesions (4 percent)
  - The prognosis may vary with different types of skin lesions being better for those with patches or plaques and worst for patients with erythrodermic or purpuric lesions.

Clinical variants

Acute

- Less common clinical features may include:
  - Interstitial pulmonary infiltrates, which may be due to pneumocystis jirovecii pneumonia
  - Central nervous system involvement with mass lesions on imaging

Clinical variants

Lymphomatous

- The lymphomatous variant accounts for approximately 20 percent of cases and is characterized by prominent lymphadenopathy without blood involvement.
- Patients frequently have an elevated LDH level and can have hypercalcemia.
- Prognosis is poor with a survival similar to that of patients with the acute variant.

Clinical variants

Chronic

- Approximately 10 percent of cases are a chronic variant.
- These patients present with skin lesions, mild lymphadenopathy, leukocytosis, and an absolute lymphocytosis that may be stable for months to years.
- Median survival is two to five years, however, there is a subgroup of patients with unfavorable chronic-type ATL, which is defined by a low serum albumin, high LDH, or high blood urea nitrogen concentration.
- These patients have a poor prognosis similar to that of the acute and lymphoma variants.

Clinical variants

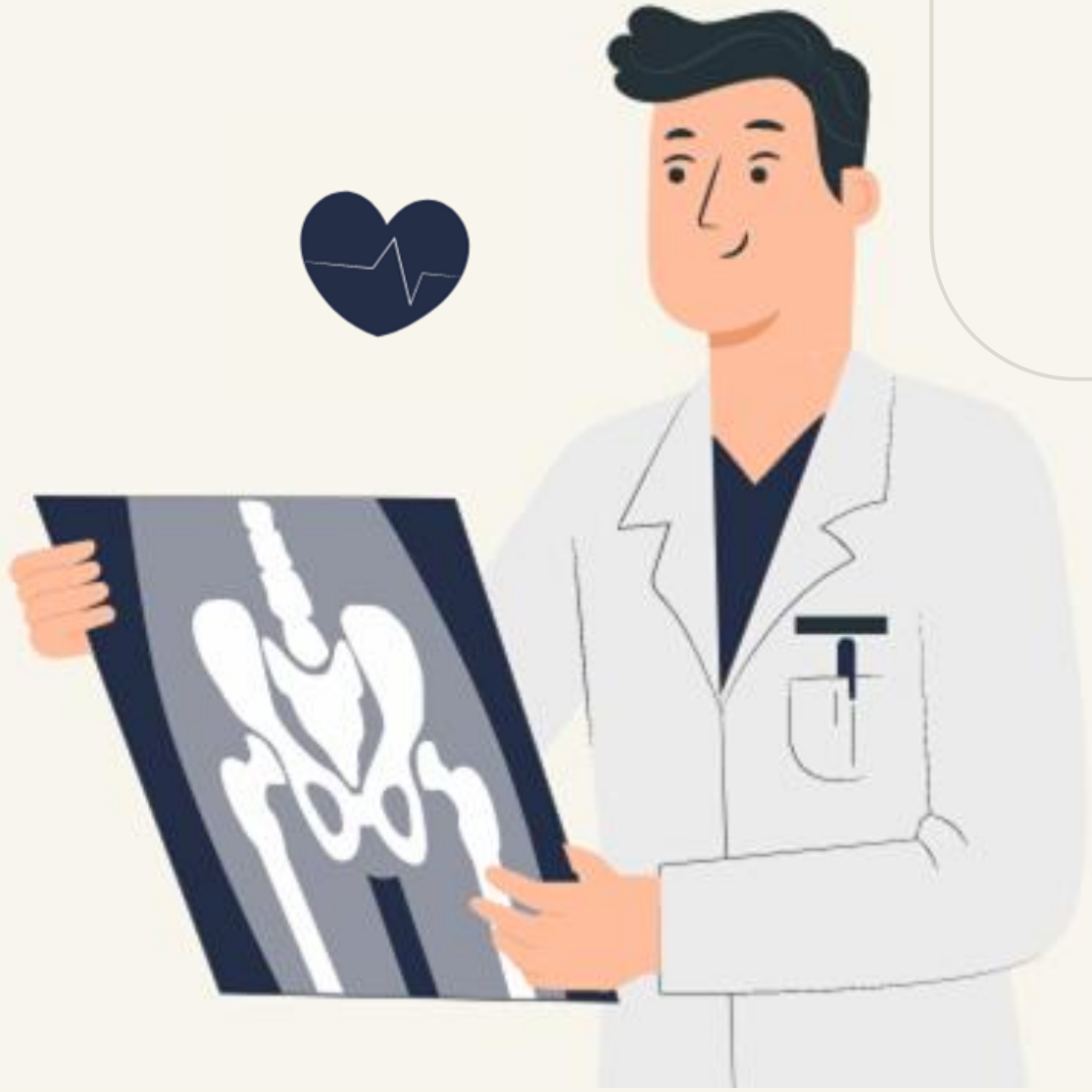
Smoldering

- The smoldering variant is least common, accounting for approximately 10 percent of cases.
- These patients are often asymptomatic except for skin and/or pulmonary lesions.
- They have normal blood lymphocyte counts with <5 percent circulating neoplastic cells and normal calcium levels.
- Median survival without treatment is approximately three years

Hypercalcemia & lytic bone lesions

As mentioned above, the frequency of hypercalcemia and lytic bone lesions differs among the variants of ATL.

In the acute variant, approximately 70 percent of patients with ATL will have hypercalcemia at some point in their disease course while 40 percent will have lytic bone lesions.



PATHOLOGY

Morphology

Lymph nodes

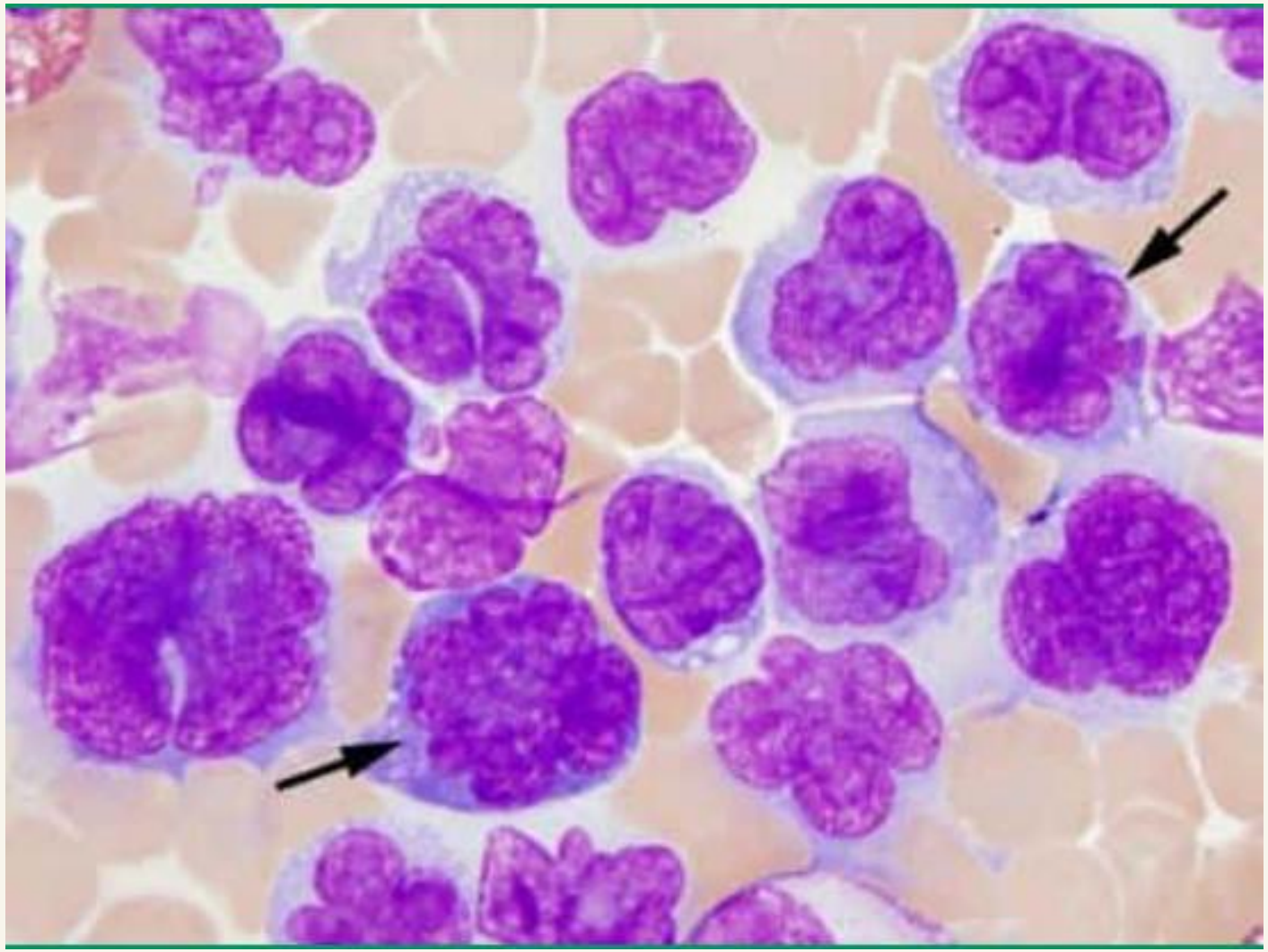
Immunophenotype

PBS & BM

Peripheral blood & bone marrow

- The most characteristic morphologic feature of ATL is seen in the peripheral blood of leukemic cases.
- In such cases, medium sized lymphocytes with condensed chromatin and bizarre hyperlobated nuclei ("clover leaf" or "flower cells") can be found, often resembling the Sézary cells of mycosis fungoides.
- Bone marrow involvement is seen in approximately 35 percent of cases.
- Bone marrow infiltrates are usually patchy, ranging from sparse to moderate.

Flower cells



Immunophenotype

- The origin of the malignant cell in ATL is a human T-lymphotropic virus, type I (HTLV-I) infected mature CD4+ T-lymphocyte.

- For purposes of diagnosis, suspected cases should be stained for CD3, CD4, CD7, CD8, and CD25 at a minimum.
- Tumor cells express T cell associated antigens (CD2, CD4, and CD5), but usually lack CD7 and may exhibit dim CD3 expression.
- Most cases are CD4+ and CD8-.
- Rare cases are CD4-/CD8+ or CD4+/CD8+.
- CD25 is expressed in a majority of the cases, as is CD52

Genetics

- **There is no distinct molecular or karyotypic abnormality in ATL other than clonally integrated HTLV-1, which is observed in all malignant cells.**
- Karyotypic analysis is generally reserved for patients enrolled in clinical trials.
- The T cell receptor genes are clonally rearranged.
- The most common karyotypic changes involve copy number alterations of 3q, 6q, and 14q, as well as inv(14).
- In three studies, the more clinically aggressive ATL variants had the most complex chromosomal abnormalities

Diagnosis

- The diagnosis of ATL is based on a combination of characteristic clinical features, morphologic and immunophenotypic changes of the malignant cells, along with confirmation of human T-lymphotropic virus, type I (HTLV-I) infection.

Diagnosis

- Identification of at least 5 percent tumor cells by cytology and immunophenotype in the peripheral blood with confirmation of HTLV-1 infection is often sufficient to make the diagnosis in patients with acute, chronic, or smoldering type ATL.

- Patients with lymphomatous lesions should undergo an excisional biopsy of an involved lymph node for histopathologic examination.

HTLV-1 infection

Practically all patients with ATL have serologic antibodies to HTLV-I. An enzyme-linked immunosorbent assay (ELISA) is the most frequently used screening test, using antigens prepared from whole virus lysate or by recombinant technology.

HTLV-1 infection

PCR-based testing to detect proviral DNA in tumor cells should be performed in the rare instance where **serology is negative but suspicion for ATL is high**.

Immunophenotype

The immunophenotype is that of an activated mature T-lymphocyte.

The most common immunophenotype is CD4+, CD25+, CD7-, and CD8-.

PRETREATMENT EVALUATION

BMA/B

Unilateral bone marrow biopsy or aspiration is recommended for all patients

LP

for all patients with acute or lymphoma-type variants

CT Scan

A contrast-enhanced computed tomography (CT) scan of the neck, chest, abdomen and pelvis should be performed.

GI workup

Endoscopy of the upper gastrointestinal (GI) tract with biopsy should be considered for all patients

EF

A study of cardiac ejection fraction (eg, echocardiogram or MUGA) should be performed if anthracyclines are used.

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DIAGNOSIS[a]

ESSENTIAL[b]:
- CBC with differential and peripheral blood smear for atypical cells[c]: lymphocytosis (ALC >4000/µL in adults) in acute and chronic subtypes[d]
- Peripheral blood flow cytometry with adequate immunophenotyping to establish diagnosis[e]
- Flow cytometry panel may include: CD2, CD3, CD4, CD5, CD7, CD8, CD25, CD30, TCRαß, TRBC1
- Assessment of HTLV-1/2 by serology or other methods[f]

USEFUL IN CERTAIN CIRCUMSTANCES:
- Biopsy of lymph nodes (excisional), skin biopsy, GI tract, or bone marrow biopsy[g] is required if:
  - Diagnosis is not established on peripheral blood, or
  - Ruling out an underlying infection (eg, tuberculosis, histoplasmosis, toxoplasmosis)
- If biopsy performed, the recommended panel for paraffin section IHC is as follows[e,h,i]: CD3, CD4, CD5, CD7, CD8, CD25, CD30
- Flow cytometry for CCR4
- Consider NGS panel

→

WORKUP

ESSENTIAL:
- H&P examination, including complete skin examination
- Comprehensive metabolic panel
- LDH
- Serology for strongyloides
- FDG-PET/CT scan[j] ± C/A/P/neck CT with contrast
- Pregnancy testing in those of childbearing potential (if chemotherapy or RT is planned)

USEFUL IN CERTAIN CIRCUMSTANCES:
- HIV testing
- Hepatitis B and C testing
- CRP, soluble interleukin-2 receptor (sIL-2R), serum albumin, and blood urea nitrogen (BUN)
- Upper gastrointestinal (GI) endoscopy
- Echocardiogram or MUGA scan if anthracycline-based regimen is indicated
- CNS evaluation: Head CT or MRI with contrast and/or lumbar puncture in all patients with acute or lymphoma subtypes or in patients with neurologic manifestations
- Uric acid
- HLA typing
- Discuss fertility preservation[k]

ATLL SUBTYPE[d]

- Smoldering subtype (ATLL-2)
- Chronic subtype (ATLL-3)
- Acute subtype (ATLL-4)
- Lymphoma subtype (ATLL-4)

INITIAL TREATMENT

Patients with *acute*, *lymphomatous*, or *unfavorable chronic* type adult T cell leukemia-lymphoma (ATL) progress quickly without treatment and have a median overall survival (OS) measured in months.

Treatment of these variants has been challenging since the tumor cells have an intrinsic resistance to most chemotherapeutic agents and because the patients have an underlying immunocompromised state associated with their HTLV-1 infection.

Multiagent regimens

The optimal chemotherapy combination for patients with ATL is unclear and many intensive regimens have been investigated.

Patients may initially respond to treatment with combination chemotherapy regimens devised for advanced, aggressive non-Hodgkin lymphoma, but relapses are common.

The median survival time for patients with acute, lymphoma-type, or unfavorable chronic-type ATL treated in prospective trials that employed multiagent chemotherapy has ranged from 5 to 13 months.

Of those evaluated in prospective trials, the regimen that appears to result in the longest median survival is **VCAP-AMP-VECP** (also known as LSG15), which includes treatment with:

- Vincristine
- Cyclophosphamide
- Doxorubicin
- Prednisone
- Ranimustine
- Vindesine
- Etoposide
- Carboplatin

The use of VCAP-AMP-VECP is supported by phase 2 and phase 3 studies

A phase 3 trial of 118 patients with poor prognosis ATL compared six courses of VCAP-AMP-VECP with eight courses of CHOP-14 (cyclophosphamide, doxorubicin, vincristine, and prednisone every 14 days).

The longer OS at 3 years and higher CR rate with VCAP-AMP-VECP compared with biweekly CHOP suggest that VCAP-AMP-VECP might be a more effective regimen at the expense of higher toxicities.

The addition of mogamulizumab (defucosylated humanized anti-CCR4 antibody) to combination therapy resulted in:

- Higher CR (52 versus 33 percent) and overall response (86 versus 75 percent) rates.
- Higher CR rates among those with blood involvement (100 versus 43 percent) or nodal/extranodal disease (92 versus 73 percent) than among those with skin lesions (50 versus 60 percent).
- Longer median progression-free survival (PFS; 8.5 versus 6.3 months).
- Higher rates of rash, infusion reactions, thrombocytopenia, lymphopenia, cytomegalovirus infection, and electrolyte disturbances.

All patients with acute, lymphoma-type, or unfavorable chronic-type ATL should be treated with combination chemotherapy.

Given a 10 to 25 percent risk for involvement of the central nervous system (CNS) at diagnosis or relapse, we recommend that all patients receive intrathecal chemotherapy for CNS prophylaxis

UpToDate®

- We suggest the use of VCAP-AMP-VECP plus intrathecal chemotherapy rather than other regimens of combination chemotherapy.

- When available, we suggest the addition of mogamulizumab to VCAP-AMP-VECP.

- This regimen requires six to eight months of weekly chemotherapy with GCSF support.

- The *ranimustine* and *vindesine* used in this regimen are not available in some countries, including the United States.

- For patients treated by clinicians who do not have access to these agents, one of the acceptable alternative regimens is hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD).

- For patients ≥70 years, we generally treat with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or a CHOP-like regimen

- If available, we suggest that mogamulizumab be given in conjunction with these regimens.

- Although some investigators have reported anecdotal experiences suggesting the efficacy of **oral etoposide**, the evidence supporting its efficacy is inadequate, and most patients with aggressive subtypes of ATL cannot be controlled with oral etoposide for a clinically meaningful duration.

- Although the randomized phase II study described above suggested that the addition of **mogamulizumab** to multiagent chemotherapy improves its anti-tumor efficacy, several observations after mogamulizumab was approved in Japan suggest an **increased risk of acute graft-versus-host disease** and transplant-related mortality in allogeneic HCT recipients previously treated with mogamulizumab.

- As an example, in a retrospective review of 996 patients who underwent allogeneic HCT for ATL, the use of pretransplant mogamulizumab was associated with an increased risk of severe (grade 3/4) graft-versus-host disease (relative risk 1.8), increased non-relapse mortality at one year (44 versus 25 percent), and inferior OS at one year (32 versus 49 percent), especially when it was used within 50 days prior to HCT

Interferon/Zidovudine (IFN/AZT)

- A meta-analysis showed that the OS rates at 5 years for frstline treatment with AZT/IFN were 28%, 0%, and 100% in patients with **acute**, lymphoma, and chronic/smoldering ATL, respectively, indicating that **leukemic subtypes** signifcantly benefted from frst-line antiviral therapy.

- The use of AZT/IFN at any time prolonged survival and was the only factor associated with a reduction in the risk of death among patients with aggressive ATL.

Arsenic trioxide

The efficacy of arsenic trioxide in combination with IFN was evaluated in ten patients with newly diagnosed chronic ATL; the ORR was 100% including a CR rate of 70%.

A retrospective study of consolidation therapy with arsenic trioxide combined with IFN/AZ reported a median duration of response of 10 months in five patients with aggressive ATL.

Arsenic trioxide is recommended by the international consensus meeting report, although it is not approved in Japan.

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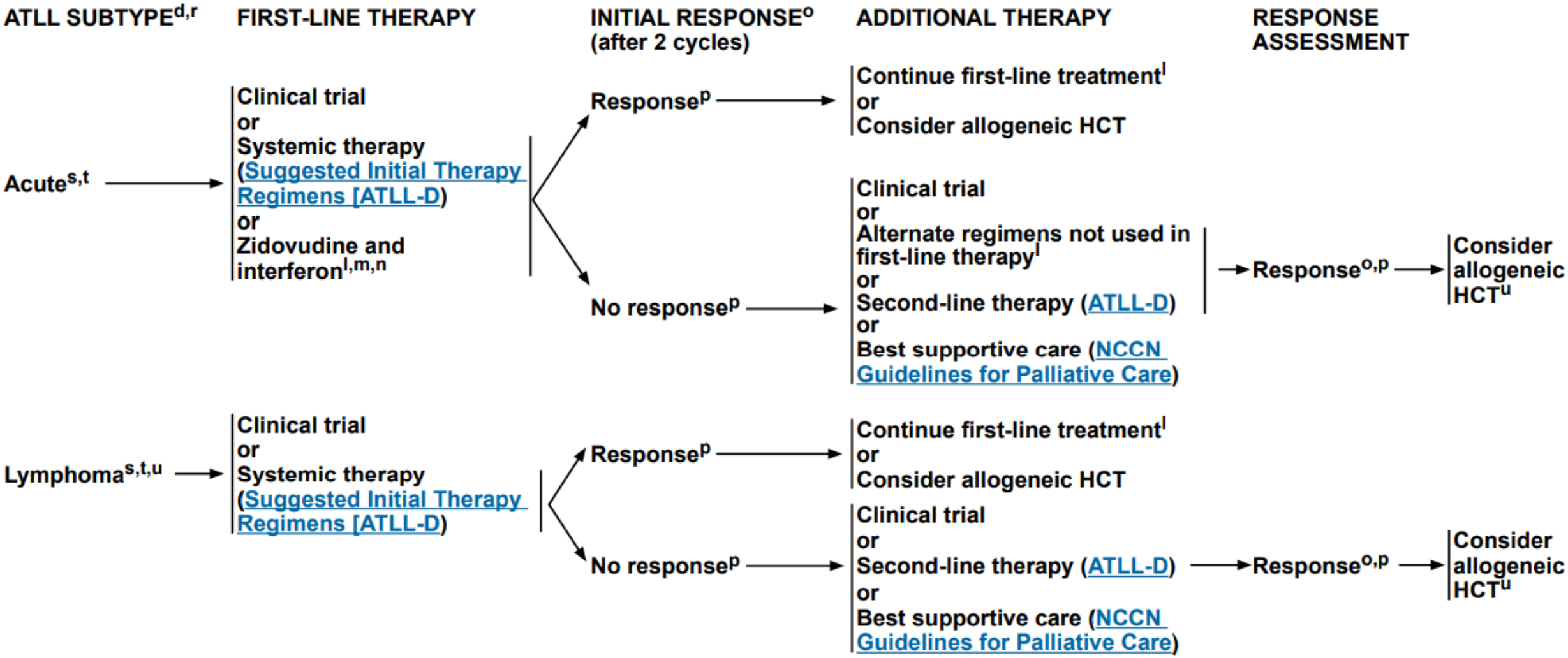

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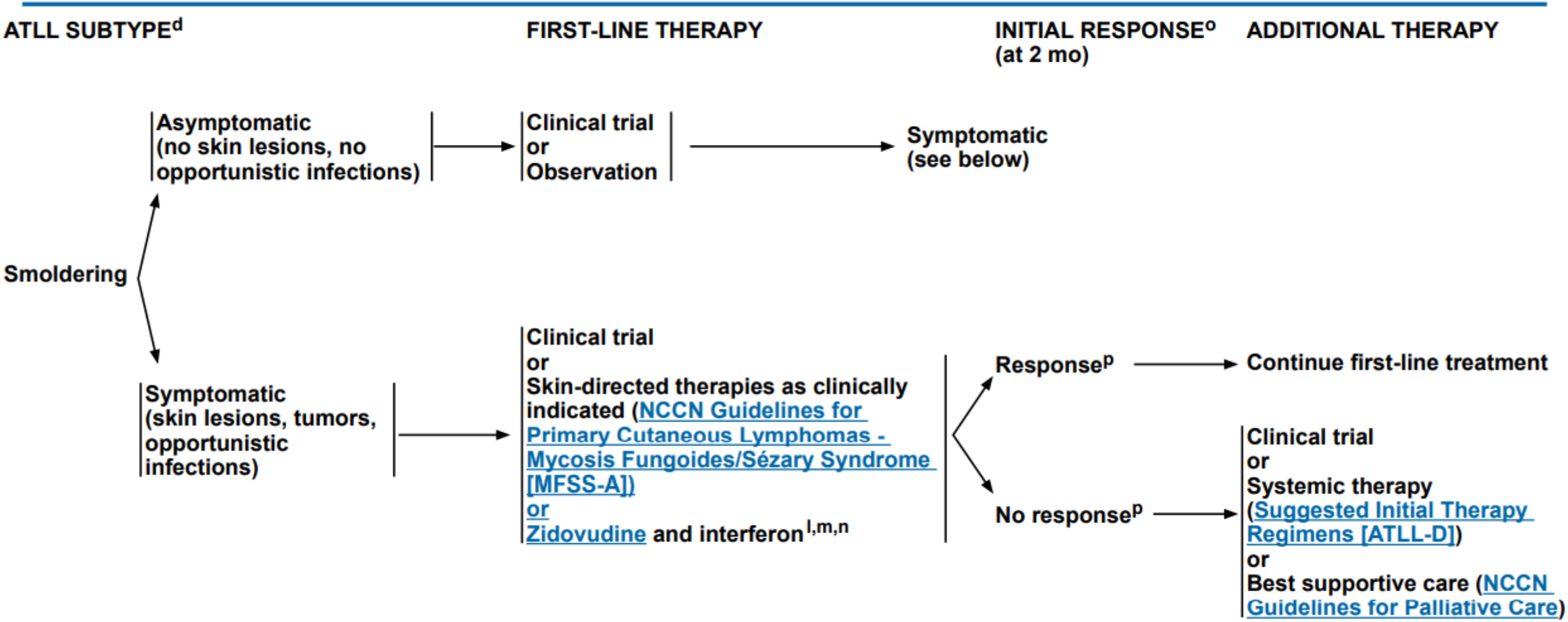

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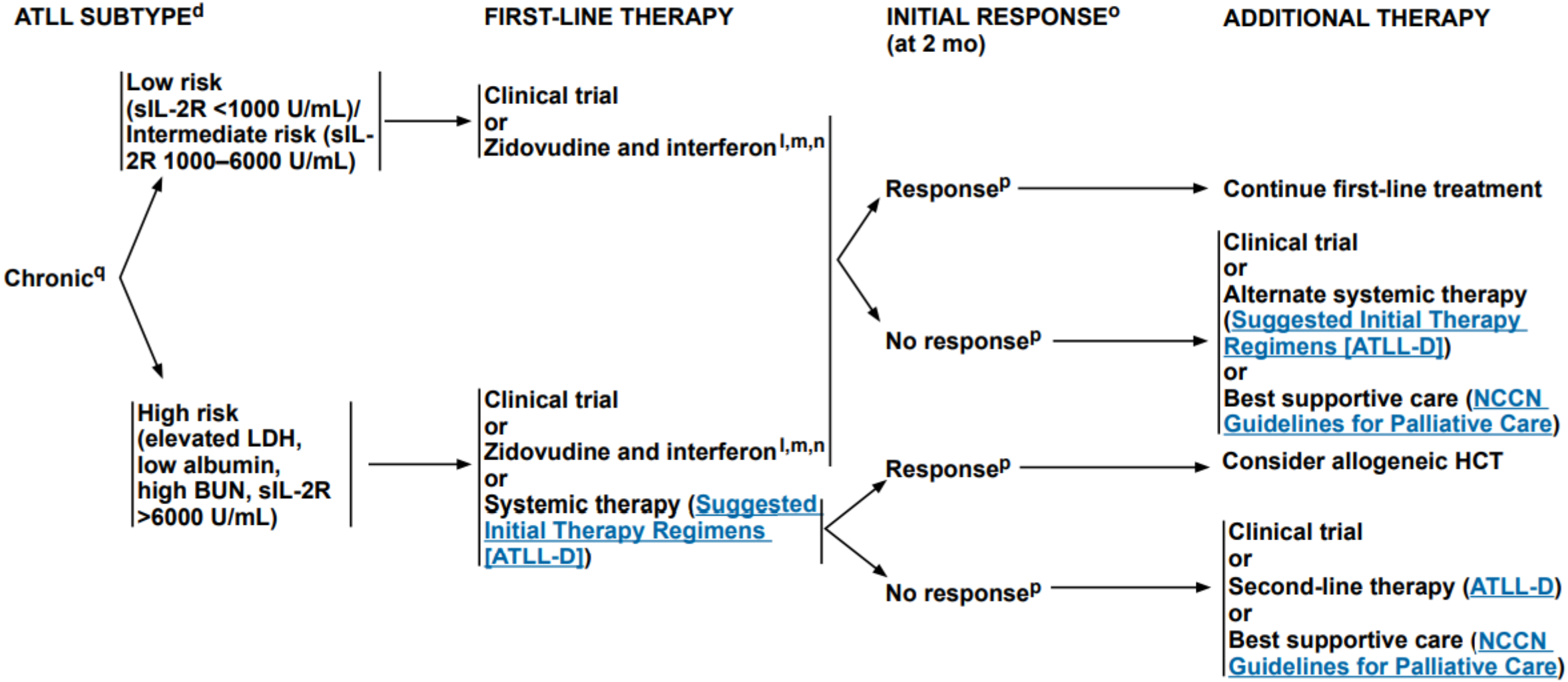


SUGGESTED TREATMENT REGIMENS[a,b]

INITIAL THERAPY

Preferred regimens (regimens in alphabetical order)
- Clinical trial
- Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone) for CD30+ cases
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)
- Zidovudine and interferon[c] (acute, chronic, and symptomatic smoldering subtypes)

Other recommended regimens (alphabetical order)
- CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone)
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine

Useful in certain circumstances
- CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) (unable to tolerate intensive regimen or non-CD30 expressing ATLL)

SECOND-LINE THERAPY OR SUBSEQUENT THERAPY

Preferred regimens (regimens in alphabetical order)
- Clinical trial
- Single agents
  - Brentuximab vedotin for CD30+ cases
  - Lenalidomide[d]
  - Mogamulizumab[d,e]
- Combination regimens
  - DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
  - ESHA (etoposide, methylprednisolone, and cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, and cisplatin)
  - GemOx (gemcitabine and oxaliplatin)
  - GVD (gemcitabine, vinorelbine, and liposomal doxorubicin)
  - ICE (ifosfamide, carboplatin, and etoposide)
  - Zidovudine and interferon[c] (acute, chronic, and symptomatic smoldering subtypes)

Alternative regimens (alphabetical order)
- Single agents
  - Alemtuzumab[f]
  - Arsenic trioxide
  - Belinostat
  - Bendamustine
  - Bortezomib
  - Gemcitabine
  - Pralatrexate
  - RT in selected cases with localized, symptomatic disease[g]

[a] See ATLL-D 2 of 2 for references for regimens.
[b] See Supportive Care (TCLYM-B) for TLS prophylaxis and anti-infective prophylaxis.

NCCN Guidelines

- In aggressive variants of ATLL ,CNS prophylaxis is recommended.
- Antiviral therapy alone is not effective.

Novel molecular targeted agents in ATL

- Mogamulizumab
- Lenalidomide
- Brentuximab vedotin
- Valemetostat
- Histone deacetylase inhibitors
- Immune checkpoint inhibitors

Mogamulizumab

A monoclonal antibody against CC chemokine receptor 4 (CCR4), was approved for patients with R/R aggressive ATL in Japan in 2012 based on the results of a phase 2 study that included 26 patients.

The ORR was 50%, and the median PFS was 5.2 months.

Lenalidomide

In a phase 2 clinical trial of lenalidomide for 26 patients with R/R aggressive ATL, the ORR, median PFS, and MST were 42%, 3.8 months, and 20.3 months, respectively.

Grade 3–4 adverse events included neutropenia (65%), lymphopenia (38%), and thrombocytopenia (23%), which were all manageable.

In Japan, lenalidomide was approved for the treatment of R/R ATL in 2017 based on these fndings.

Brentuximab vedotin

BV is currently available for patients with PTCL including ATL in Japan, although further studies are needed to assess the efficacy and safety in patients with ATL

Valemetostat

A phase 2 clinical trial assessed the efficacy and safety of *valemetostat* in 25 patients with R/R aggressive ATL.

The ORR was 48.0% including five complete and seven partial remissions.

Grade 3–4 adverse events included thrombocytopenia (32%), anemia (32%), lymphopenia (16%), and neutropenia (12%), which were all manageable.

This study resulted in the approval of valemetostat for clinical use in Japan for patients with R/R aggressive ATL in September 2022

Histone deacetylase inhibitors

In a phase 2 clinical trial of tucidinostat for 23 patients with R/R aggressive ATL, the ORR and median PFS were 30.4% and 1.7 months, respectively.

Grade 3–4 adverse events included thrombocytopenia (39%), neutropenia (39%), anemia (17%), and lymphopenia (4%), which were all manageable.

These results led to the approval of tucidinostat for R/R aggressive ATL in Japan.

Immune checkpoint inhibitors

In a US phase 2 trial of nivolumab, a fully human IgG4 monoclonal antibody inhibitor of PD-1, rapid disease progression was observed in all three patients after a single dose of nivolumab, and the clinical trial was terminated.

A phase 2 trial of nivolumab for patients with R/R aggressive ATL in Japan did not show such a clinical course, and the study is currently ongoing.

Tax-DC

The vaccine with Tax peptide-pulsed dendritic cell (Tax-DC) was designed to promote the HTLV-1 Tax specific cytotoxic T-lymphocyte (CTL) response.

A pilot study of the Tax-DC vaccine reported long Tax-specific CTL responses with peaks at 16–20 weeks in all three patients who were previously treated and achieved PR or stable disease.

Two patients achieved partial remission in 8 weeks, one of whom later achieved complete remission, and one achieved stable disease in 8 weeks.

Further study will be required to confirm the efficacy of the vaccine as a maintenance therapy for ATL.

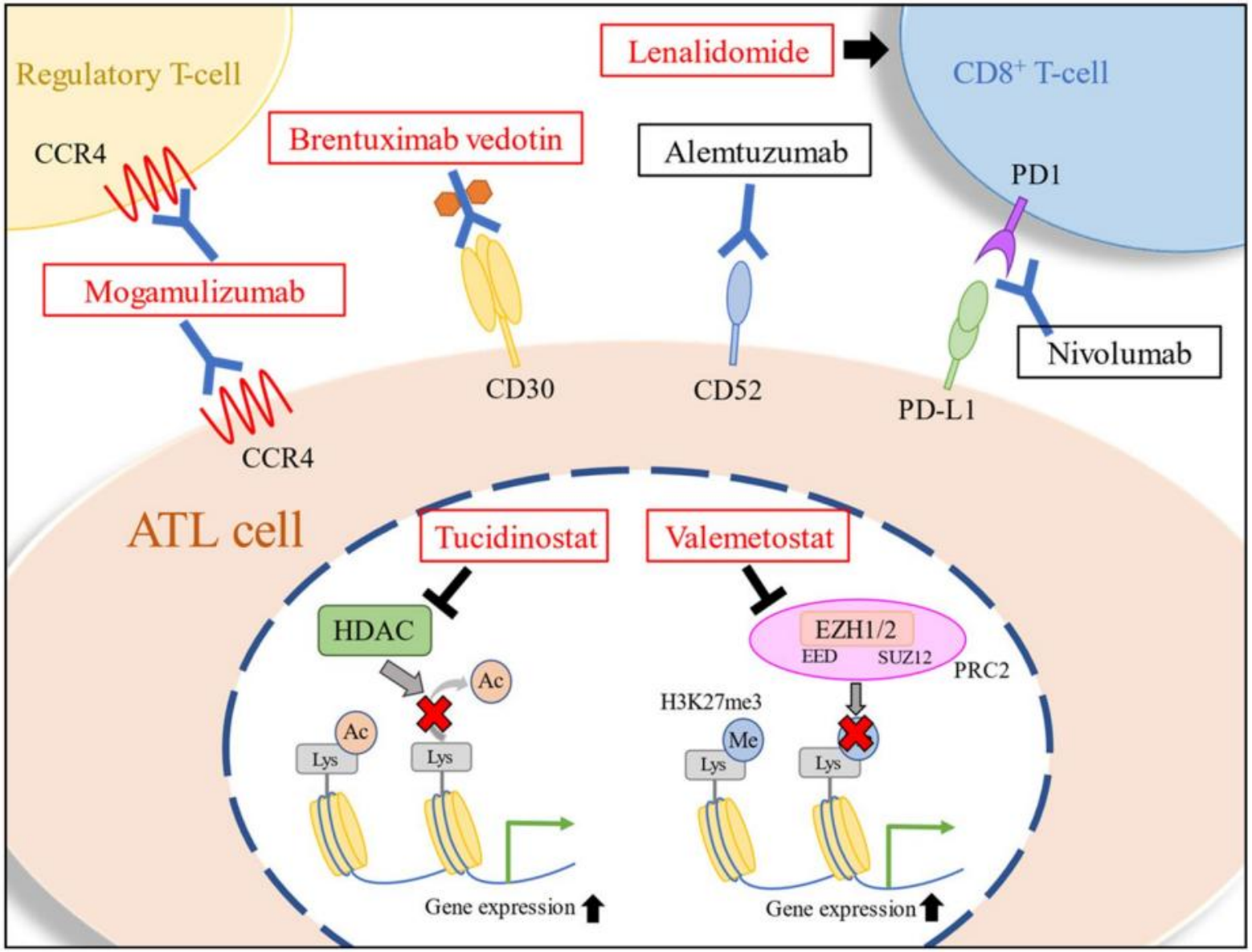
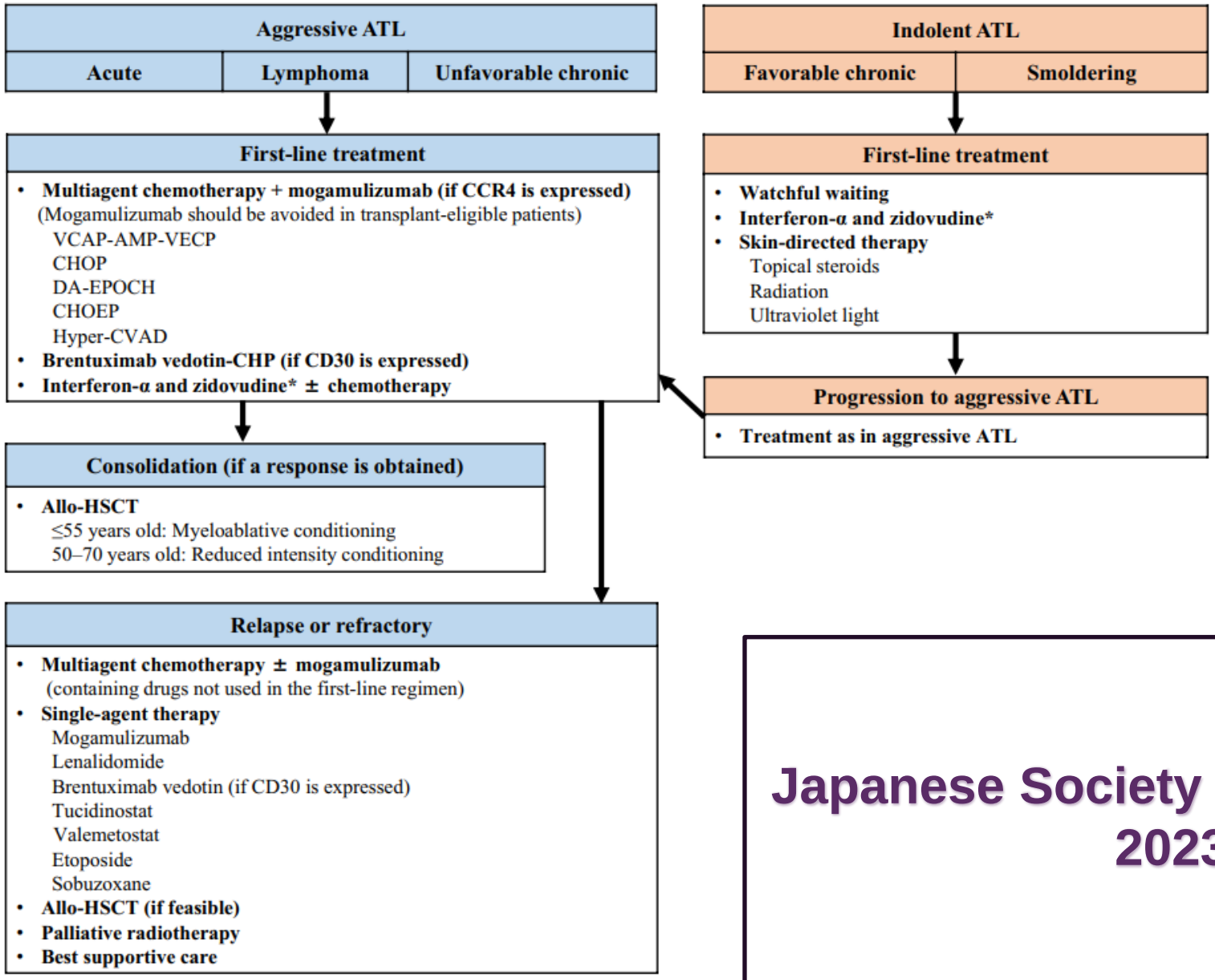


Fig. 2 Current and potential molecular targeted therapies in ATL. Agents that are approved and not approved in Japan are colored in red and black, respectively. Mogamulizumab targets CC chemokine receptor 4 on the surface of both ATL cells and regulatory T-cells. Brentuximab vedotin is a human CD30-directed chimeric antibody bonded to the microtubule-disrupting agent. Alemtuzumab is a humanized monoclonal antibody against CD52. Nivolumab is a human monoclonal antibody against programmed death-1. Tucidinostat is a benzamide histone deacetylase (HDAC) inhibitor. Valemetostat is an enhancer of zeste homolog 1 (EZH1) and EZH2 dual inhibitor



Japanese Society of Hematology 2023


Complications
of
therapy

- The treatment of patients with ATL requires close attention to the following issues that often surround chemotherapy administration:

Opportunistic infections:

- Patients with ATL are immunocompromised and are therefore at risk for potentially lethal opportunistic infections with organisms such as *Pneumocystis jirovecii* (previously P. carinii), *Candida*, *cytomegalovirus*, *disseminated cryptococcus*, and *Strongyloides stercoralis*.

- We routinely administer oral trimethoprim-sulfamethoxazole (TMP-SMX) for P. jirovecii pneumonia (PCP) prophylaxis.

- In addition, we administer antifungals to all patients receiving chemotherapy for ATL.

- Anti-strongyloides agents are given to patients with a past and/or present exposure to the parasite in the tropics.

- The treatment of patients with ATL requires close attention to the following issues that often surround chemotherapy administration:

Hypercalcemia:

- Which can be severe, is one of the most significant complications in ATL patients.
- There is no routine prophylaxis given, but patients must be followed closely so that treatment can be initiated emergently.

- The treatment of patients with ATL requires close attention to the following issues that often surround chemotherapy administration:

Tumor lysis syndrome:

- is best prevented with aggressive intravenous fluid hydration to insure a high urine output, *rasburicase* or *allopurinol*, and correction of electrolyte disturbances and elements of reversible renal failure

- The treatment of patients with ATL requires close attention to the following issues that often surround chemotherapy administration:

Antiviral therapy:

- The benefit of antiviral agents in ATL is controversial. Small, prospective trials and retrospective analyses performed outside of Japan have evaluated the use of the antiviral agent zidovudine (AZT) plus interferon alfa in the treatment of newly diagnosed or relapsed ATL.

- Median survival with this regimen have ranged from 6 to 18 months.

Antiviral therapy:

- A 2010 meta-analysis of AZT plus interferon alfa incorporated data from 245 patients with acute (47 percent), chronic (7 percent), smoldering (4 percent), or lymphoma-type (42 percent) ATL.

- For the 207 patients whose first-line therapy was recorded, the following five-year OS rates were reported:

  - AZT plus interferon alfa (75 patients) – 46 percent
  - Chemotherapy (77 patients) – 20 percent
  - Chemotherapy followed by antiviral therapy (55 patients) – 12 percent

Conclusion

- Patients with acute, chronic, and smoldering ATL appeared to benefit from first-line antiviral therapy, whereas patients with lymphoma-type ATL did not.
- For patients with chronic or smoldering ATL, this combination was reported to result in 100 percent five-year survival.
- Based on the results of this retrospective analysis, the investigators suggested this combination regimen as the first-line therapy in leukemic subtypes of ATL.

- The treatment of patients with ATL requires close attention to the following issues that often surround chemotherapy administration:

Hematopoietic cell transplantation:

- Both autologous and allogeneic hematopoietic cell transplantations (HCT) have been evaluated in patients with ATL.
- Allogeneic HCT offers a potential graft-versus-leukemia effect and may be considered for patients with an available donor.
- There is limited experience with autologous HCT for ATL, but it does not appear reduce early relapses.

Hematopoietic cell transplantation:

- A number of small studies have evaluated the role of myeloablative and nonmyeloablative allogeneic HCT in this disorder. (…continue)

- Treatment-related mortality was high, although long-term survival was achieved in some patients, with potential evidence of a graft-versus-HTLV-1 and a graft-versus-tumor effect.

- After allogeneic HCT, HTLV-1 provirus load was significantly decreased in some patients, suggesting that anti-HTLV-1 immune response is enhanced in these patients.

Hematopoietic cell transplantation:

- Retrospective data are available from Japan regarding 586 patients with ATL who underwent allogeneic HCT between 1992 and 2009.
- For the 280 patients who underwent myeloablative conditioning, median OS and estimated three-year survival were 9.5 months (95% CI 6.7-18.0 months) and 39 percent (33 to 45 percent), respectively.
- Corresponding values for the 306 patients who underwent reduced intensity conditioning were 10 months (7.2 to 14.0 months) and 34 percent (29 to 40 percent), respectively.
- When compared with myeloablative conditioning, reduced intensity conditioning was associated with a trend toward less treatment-related mortality (hazard ratio [HR] 0.786; 95% CI 0.538-1.148), but greater leukemia-related mortality (HR 1.579; 95% CI 1.080-2.308). (…continue)

Hematopoietic cell transplantation:

- Early transplantation within 100 days after diagnosis might improve the survival of patients with aggressive ATL.
- Although allo-HSCT can represent a cure for specific patients with aggressive ATL, high treatment-related mortality (TRM) is a big concern.
- Several retrospective studies showed that the OS rates and relapse rates in patients treated with reduced-intensity conditioning (RIC) were similar to those in patients treated with myeloablative conditioning.
- The RIC regimens are preferred in patients 50 years of age or older. (…continue)

Hematopoietic cell transplantation:

- The disease status at the time of HCT impacts outcome.
- In a retrospective analysis of 214 Japanese patients with acute or lymphomatous subtypes of ATL who underwent allogeneic HCT, the median survival time was 5.9 months and 26 percent were alive at four years post-HCT.
- The median survival time was significantly longer for those transplanted in first remission (22 months) when compared with those with primary refractory (4 months) or relapsed disease (3 months). (…continue)

Hematopoietic cell transplantation:

- Another retrospective analysis included 40 patients with acute or lymphoma-type ATL who had undergone allogeneic HCT either as part of their initial therapy or at relapse.
- All but one of the patients was treated with a myeloablative conditioning regimen.
- At the time of transplant, 15 were in CR, 13 in partial remission (PR), 3 had stable disease, and 9 had progressive disease.
- Of the patients evaluable after HCT, all but one achieved a CR.
- The median survival time of all cases after HCT was 9.6 months.

Continue…

- There were 16 deaths related to transplant. The three-year rates of OS and relapse-free survival were 45 and 34 percent, respectively.
- Acute and chronic graft-versus-host disease developed in 26 and 15 patients, respectively.
- Among the 10 patients who relapsed after HCT, five were able to achieve a second CR.
- Three of these CRs were obtained by reduction or cessation of immunosuppressive therapy alone suggesting a graft-versus-ATL effect.

Hematopoietic cell transplantation:

- A multicenter study of HLA-haploidentical HCT with post-transplantation cyclophosphamide (PTCy) in 18 patients was associated with 83 percent one-year overall survival (OS) and 73 percent two-year OS.
- Rates of overall survival (OS) were 83 percent at one year and 73 percent at two years.
- One-year non-relapse mortality (NRM) and disease progression were 11 percent and 28 percent, respectively.
- For patients who do not have suitable HLA-matched related donors or cannot await coordination for an unrelated donor, cord blood transplantation (CBT) or haploidentical HSCT (haplo-HSCT) are alternative stem cell sources.
- Retrospective data of CBT indicated high TRM rates (10–46%) and poor prognosis.
- **Haplo-HSCT with PTCy for aggressive ATL might be a potential option for patients without suitable HLA-matched related donors.**

Thanks