BHS guidelines for the treatment of large granular lymphocyte and chronic prolymphocytic leukaemias

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Large granular lymphocyte and prolymphocytic leukaemias are rare chronic lymphoproliferative disorders. Large granular lymphocyte leukaemias consist of indolent disorders such as T-cell large granular lymphocyte and chronic lymphoproliferative disorder of natural killer cells and the very rare but aggressive natural killer cell leukaemia. Treatment of the indolent large granular lymphocyte leukaemias is necessary in case of symptomatic cytopaenias or non-haematological autoimmune disorders. First line therapy of these two disorders is based on three immunosuppressive drugs: methotrexate, cyclophosphamide and cyclosporine A. Aggressive natural killer cell leukaemia needs an L-asparaginase containing regimen as induction followed by allogeneic stem cell transplantation to prolong remission. T-cell prolymphocytic leukaemia always follows an aggressive course even after an indolent onset. The optimal treatment strategy should exist of remission induction with alemtuzumab intravenously followed by autologous or allogeneic stem cell transplantation. Treatment indications for B-cell prolymphocytic leukaemia follow the criteria described by the chronic lymphocytic leukaemia guidelines. After induction with fludarabine, cyclophosphamide, rituximab or bendamustine in patients without a p53 mutation and/or a 17p deletion and alemtuzumab in case of a p53 mutation and/or a 17p deletion, stem cell transplantation must be considered.

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Part I: Large Granular Lymphocyte Leukaemias

Large granular lymphocytes (LGLs) represent 10-15% of normal peripheral blood mononuclear cells. LGLs are large lymphocytes showing an eccentric nucleus and abundant cytoplasm with typical azurophilic granules. They are derived from two different lineages: 85% are CD3+ CD56- CD57+ T cells and represent antigen activated cytotoxic T lymphocytes, whereas the remaining 15% are CD3- CD56+ CD57- Natural Killer (NK) cells.[1] Dysregulation of cell signalling pathways, particularly the JAK/STAT3 axis, leads to loss of apoptosis and to proliferative disorders of these LGL cells.[2] Following the 2008 WHO classification of tumours of hematopoietic and lymphoid tissues, LGL leukaemias encompass three distinct entities (*Table 1*):

- T cell LGL leukaemia, consisting of a clonal proliferation of CD3+ LGLs.
- Aggressive NK-cell leukaemia, corresponding to an accumulation of NK CD3- LGL cells with an aggressive behaviour.
- Chronic lymphoproliferative disorder of NK cells, a chronic and indolent CD3- LGL lymphocytosis. It is not clear whether this entity represents a benign disorder or a chronic phase of NK cell LGL leukaemia.

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Table 1. Characteristics of T-LGL, aggressive NK leukaemia and T-PLL.

	T-LGL	Aggressive NK-L	T-PLL
Median age	60 y	39 y	65 y
Clinical course	Indolent	Very aggressive	Aggressive
Clinical features	Splenomegaly, cytopaenia, auto-immune manifestations	Hepatosplenomegaly, B symptoms, lymphadenopathies, severe cytopaenia, multi-organ failure	Hepatosplenomegaly, lymphadenopathies, skin manifestations, pleuro-peritoneal effusions
Peripheral lymphocytosis	> 2000/mm^3	>10000/mm^3	>100000/mm^3
		EBV infection association	
Morphology	Large lymphocytes	Large lymphocytes	Medium sized lymphocytes
	Abundant cytoplasm with azurophilic granules	Abundant cytoplasm, azurophilic granules	Basophilic cytoplasm with blebs
	Eccentric nucleus	Eccentric nucleus	Round nucleus with nucleolus
			Small cell and cerebriform variants
Immunophenotype	CD3$^+$ CD8$^+$ CD16$^+$ CD57$^+$	CD3$^-$, CD8$^+$, CD4$^-$	CD2$^+$, CD3$^+$, CD5$^+$
	CD56$^-$ CD28$^-$	CD56$^+$, CD16$^+$	CD7^{++}; CD52^{++}
	TCR αβ$^+$; 10% TCR γδ$^+$	TCR αβ$^-$; TCR γδ$^-$	CD4/CD8 variable
			CD1a$^-$; TdT$^-$
Cytogenetics			t(14;14); inv 14; t(X;14); iso8q
Molecular biology	Clonality of TCR γ chain rearrangement	–	Clonality of TCR γ chain rearrangement
			TLC-1; MTCP-1; ATM JAK3, STAT5b

Presentation and diagnosis

T-cell LGL leukaemia

LGL leukaemia represents 2-5% of the chronic lymphoproliferative diseases in western countries and up to 6% in Asia. Indolent T-LGL represents the more frequent disorder of the group occurring in 85% of cases.[3] The disease affects men and women in the same proportion at a median age of 60 years (y) with only 10% being younger than 40 y.[4]

T-LGL leukaemias have an indolent course with a median overall survival (OS) of more than ten years. Rare aggressive forms have been described and generally affects younger people.[5] Cytopaenias, recurrent bacterial infections, autoimmune disorders and splenomegaly are the main clinical manifestations of the disease. Up to 80% of the patients with T-LGL leukaemia present with neutropenia, which can be either asymptomatic or associated with recurrent bacterial infections.[4,6] Anaemia is observed in 50% of T-LGL patients and may be secondary to pure red cell aplasia (PRCA) or autoimmune haemolytic anaemia. Thrombocytopenia is moderate and less frequent (20%), including cases of immune thrombocytopenic purpura.[4,6] Rheumatoid arthritis is the most commonly associated non-hematologic autoimmune disorder, occurring in around 30% of cases.[4,6] Other autoimmune diseases are described as case reports.[7] Finally, association with B cell lymphoid neoplasms and myelodysplasia is also observed.[7] B symptoms are mentioned in 20-40% of patients.

Sustained (> 6 months) expansion of clonal T-LGLs in peripheral blood with a characteristic immunophenotype and typical symptoms or associated immune diseases, establishes the diagnosis of T LGL leukaemia. Most patients have T-LGLs above 2000/mm^3 but a lower count does not exclude the diagnosis, especially in symptomatic patients. The demonstration of bone marrow infiltration with monoclonal LGLs can be helpful in the diagnosis of these patients.[8] The typical immunophenotype corresponds to activated cytotoxic T cells expressing CD3, CD8, CD16, CD57, TCR αβ and no expression of CD56, CD28 and CD4. Some cases, however, express CD4 with or without CD8, and around 10% are TCR γδ. Clonality is usually demonstrated using polymerase chain reaction analysis of the TCR -γ-chain rearrangement but studies of the TCR β chain variable domain repertoire with flow cytometry is another possibility in assessing monoclonality.[7]

Aggressive NK cell leukaemia

Aggressive NK cell leukaemia is a rare disease making up about 10% of the LGL proliferations with a significantly greater incidence in Asia. The patients are younger than in T LGL leukaemia (median age 39 y) and EBV infection is commonly associated with the disease.[3,9] Aggressive NK cell leukaemia presents as an acute illness with B symptoms, significant lymphocytosis, hepatosplenomegaly, lymphadenopathy and severe cytopaenia. Liver dysfunction, multi-organ failure and hemophagocytosis may occur. The median OS is only two months.[9] These LGLs show the following immunophenotype: CD3-, CD4-, CD8+, TCRαβ -, TCR γδ-, CD16+, CD56+. Clonality is more difficult to demonstrate except in the case of cytogenetic abnormalities.

Chronic lymphoproliferative disorder of NK cells

Chronic lymphoproliferative disorder of NK cells is also an indolent disease with good prognosis that represents 5% of all LGL expansions. Clinical and haematological features are similar to T LGL leukaemia except that circulating LGLs present a NK phenotype (CD3-, CD4-, CD8-, CD16+, and CD56+).[10]

Treatment (*Table 2*)

T LGL leukaemia and chronic lymphoproliferative disorder of NK cells

As T LGL leukaemia and chronic lymphoproliferative disorder of NK cells have a similar indolent evolution, indications for treatment and therapeutic options are also similar.

Indications for treatment

- Severe neutropenia (< 500/mm^3)
- Moderate neutropenia (> 500/mm^3) with recurrent infections
- Symptomatic or transfusion dependent anaemia
- Severe thrombocytopenia (< 50,000/mm^3)
- Associated non-hematologic autoimmune disorder requiring therapy

Frontline treatment

There is no well-defined standard of care for LGL leukaemias and recommendations are essentially established on the basis of small retrospective case-series. However, a recent phase II prospective multicentre trial of the Eastern Cooperative Oncology Group (ECOG) brings some new information about how to treat these patients.[11] First line therapy is based on three immunosuppressive drugs: methotrexate (MTX), cyclophosphamide (C) and cyclosporine (CyA). Clinician's choice is guided by comorbidities and associated autoimmune manifestations:

Methotrexate

In the above mentioned ECOG study, oral MTX administered at a dose of 10 mg/m^2 once a week induced an overall response rate (ORR) of 38% (95% confidence interval (CI) 26-53%). These results are in line with the retrospective analysis of the French cohort of LGL leukaemia.[4]

In practice, MTX is given at a dose of 10 mg/m^2, once weekly until progression or intolerance. As the response is slow to develop, the treatment must be continued for at least four months before stopping due to inefficiency. MTX is the recommended drug in case of associated autoimmune disease (RA). Prednisone can be associated during the first month to accelerate the response.

Cyclophosphamide

In a recent retrospective series of 45 previously untreated LGL patients, an ORR of 71% was observed with C. Relapse occurred in only 13% of the patients during the median follow up of 35 months (mo) (range 3,8-277 mo).[12] As second line treatment, in case of no response to methotrexate, the ORR to C still reached 65%.[4,11] Altogether, these results compare favourably with the ORR obtained in first line with MTX but to date, results of a randomised prospective trial assessing MTX versus C in first line therapy are not available.

In practice, C is given orally at a dose of 100 mg each day with the possibility to decrease to 50 mg in respond-

Table 2. Treatment of LGL leukaemias.

T-LGL and chronic lymphoproliferative disorder of natural killer (NK) cells		
Drug	**Schedule**	**Indications**
Cyclophosphamide (C)	• 100mg/day orally • Max 12 months	• First choice • Pure red cell aplasia
Methotrexate (MTX)	• 10mg/m^2 once a week • Until progression or toxicity	• Preferential drug in rheumatoid arthritis
Cyclosporine (CyA)	• 5 -10 mg/kg in 2 divided doses • Therapeutic level: 200 to 400 ng/ml until response then tapering to the lowest effective dose	• Pure red cell aplasia • HLA DR4 phenotype
Purine analogues		• Refractory disease
Alemtuzumab		• Refractory disease
Splenectomy		• Refractory disease with splenomegaly and /or immune cytopaenia
Aggressive NK leukaemia		
L-Asparaginase	• SMILE protocol • L-Asparaginase monotherapy	• Consolidation with allogeneic SCT

Table 3. Treatment of PLL.

T-PLL		
Drug	**Schedule**	**Indications**
Alemtuzumab	• First week dose escalation 3-10-30mg, afterwards 30mg, 3x/week • IV route of administration • Premedication required • Pneumocystis and Herpes prophylaxis • CMV monitoring	• First line therapy • Consolidation with auto/allogeneic SCT
Pentostatin + Alemtuzumab		• Suboptimal response to single agent Alemtuzumab • Effusions / Liver infiltration
Bendamustine		• Refractory disease
Purine analogues		• Refractory disease
B-PLL		
FCR / BR		• Absence of TP53 mutation • Consider consolidation with auto/allogeneic SCT
Alemtuzumab		• Presence of TP53 mutation • Consider consolidation with auto/allogeneic SCT
BCR inhibitors / New anti-CD20mAb		• To be evaluated

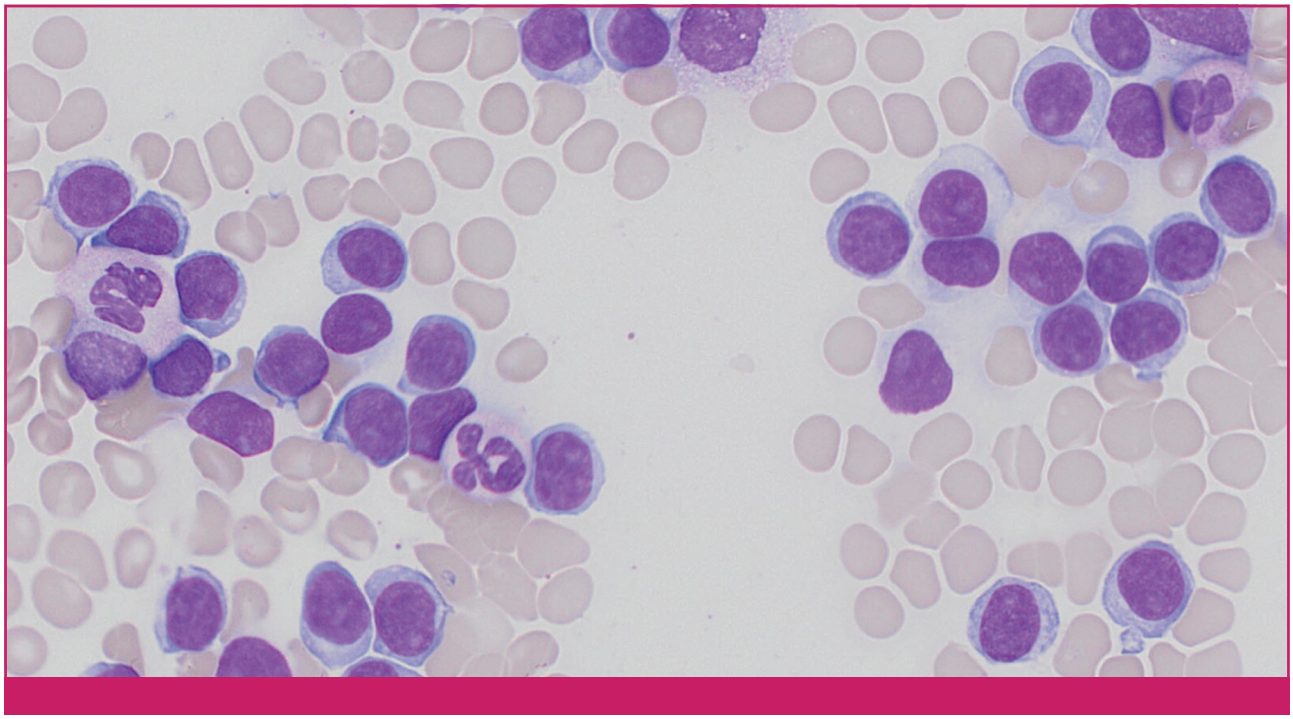

Figure 1. Morphology of T-PLL. Male, 62 y, night sweats, diffuse lymphadenopathies and splenomegaly; white blood cell count 213,000/mm3 with 90% atypical lymphoid cells (medium-sized cells with abundant basophilic cytoplasm, round to oval nuclei with fine chromatin and clear nucleoli and a regular nuclear and cytoplasmic outline); immunophenotype: CD2, CD4, CD5, CD7, cyCD3 positive, TdT, Cd1a, CD8, TCR αβ and TCR γδ negative; conventional karyotype showed typical T-PLL aberrations: 46,XY,t(4;15)(q13;p13),+i(8)(q10),del(11)(q13),inv(14)(q11q32),-22[2]46,XY[8].
Courtesy of Dr C. Brusselmans, UZ Leuven.

ing patients. The duration of treatment is minimum four months and maximum nine to twelve months to avoid secondary toxicity. Of note, C has shown particular efficacy in cases of PRCA.[13,14]

Cyclosporin

CyA is a therapeutic alternative in cases of MTX/C failure. Doses up to 5-10 mg/kg a day in two divided doses are progressively introduced and adapted to maintain a therapeutic level between 200-400 ng/ml. ORR is variable according to the reported case series with a medium ORR of 56% (range 21-100%). At response, CyA is slowly tapered to the lowest effective dose.[14-16] However, it is advised to maintain CyA unless emergence of side effects. The drug seems of particular interest in patients suffering from PRCA or having a HLA DR4 phenotype.[15]

Treatment of relapsed or refractory disease

Relapsed disease can be either retreated with the same drug or with one of the two other major immunosuppressive drugs, depending on the time of relapse. A patient resistant to one of these drugs may respond to one of the others. In refractory disease with no response to MTX, C and CyA, several alternative solutions may be considered.

Purine analogues (fludarabine, pentostatin, or 2-CDA) showed ORR up to 80% in a retrospective series of LGL patients but the results have to be considered with caution because of the very small number of reported case series.[7] **Alemtuzumab (A)** can be considered in case of failure to purine analogues if leukemic cells express CD-52, bearing in mind the high risk of opportunistic infections. **Splenectomy** may be helpful in refractory patients with symptomatic splenomegaly or autoimmune cytopaenia. Myeloid **growth factors** can be used in case of febrile neutropenia. CHOP or CHOP-like regimens seem ineffective. Finally, **inhibitors of JAK/STAT pathway** are new emerging drugs with promising activity to induce apoptosis in LGL leukemia.[17,18]

Treatment of NK cell aggressive leukaemia

NK cell aggressive leukaemia has a very poor prognosis characterised by chemo-resistance. Prompt diagnosis

and treatment are of primordial importance in this rare but rapidly fatal disease. L-asparaginase monotherapy or L-asparaginase containing regimens (SMILE protocol) followed by allogeneic stem cell transplantation (SCT) have been shown to induce prolonged remissions.[19-22]

Part II: Chronic Prolymphocytic Leukaemia

T cell prolymphocytic leukaemia

Presentation and diagnosis

T cell prolymphocytic leukaemia (T-PLL) is a rare post-thymic T cell neoplasm. This haematological malignancy represents around 2% of mature lymphocytic leukaemia in adults and up to 30% of mature T-cell neoplasms with leukemic presentation.[23,24] T-PLL has a median age of 65 y at diagnosis with a male to female ratio of 2:1.[25] A higher incidence is seen in patients suffering from the genetic disorder ataxia telangiectasia; the median age at onset in this condition is much younger.[26] Clinical course is mostly aggressive, although some patients may have an initial indolent phase. Major lymphocytosis (> 100,000/mm^3 with 90% prolymphocytes), hepatosplenomegaly, and lymphadenopathies are typical signs at presentation.[27] Skin manifestations such as nodular lesions, maculopapular rash or, more rarely, erythroderma are described. Pleuro-peritoneal effusions, peri-orbital or conjunctival oedema and central nervous system infiltration may occur.[24,27]

T-PLL identification should be based on the integration of clinical manifestations, morphological description of the peripheral blood film, flow cytometry and genetic analysis. Typical T prolymphocytes (T-PL) are medium-sized cells with round to oval nuclei and visible nucleoli (*Figure 1*). Cytoplasm is moderately abundant, basophilic without granules and may present protrusions (blebs). Less frequently, cells are small with invisible nucleoli (small cell variant; 20%) or have an irregular nuclear outline resembling the cerebriform nucleus of Sézary cells (cerebriform variant).[27] T-PL have a mature post-thymic phenotype (TdT-, CD1a-, CD5+, CD2+, or CD7+). Of note, CD7 expression seems more intense in T-PLL compared to other mature T cell leukaemias. Sixty percent of cases are CD4+/CD8-; 25% CD4+/CD8+ and 15% CD4-/CD8+. All cases express CD3 and TCRβ as surface or intracytoplasmic T cell markers. T-PL express intensively the CD52 membrane protein.[25,27] T cell receptor genes are clonally rearranged. Abnormalities of chromosome 14 are seen in 90% of T-PLL and lead to the expression and activation of the proto-oncogene TLC1 (inv(14), t(14;14)(q11;q32)) or its homolog MTCP1 (t(X;14)(q28;q11)).[28,29] Abnormalities of chromosome 8 (t(8;8), trisomy 8q, idic(8p11)) are seen in approximately 66% of patients and may lead to c-myc overexpression.[30] Other recurrent cytogenetic defects described involve several chromosomes (6, 9, 12, 17, 22, etc.).[24] Molecular investigations may identify ATM gene deletions or missense mutations as well as activating mutations of JAK1 and JAK3 tyrosine kinase. Moreover, a recent T-PLL genomic sequencing study identified recurrent mutations in the IL-2 Rγ-JAK1-JAK3-STAT5 signalling pathway offering hope for new therapeutic strategies.[31]

Treatment

With conventional alkylating-based chemotherapy prognosis of T-PLL is poor with OS of less than one year.[27] Today, the optimal treatment strategy should exist of remission induction with intravenous (IV) alemtuzumab followed by autologous or allogeneic SCT as consolidation whenever possible.[23] Alemtuzumab IV has demonstrated a high ORR and CR in pre-treated (ORR 51-76%, CR 40-60%) and in untreated patients (ORR 91%, CR 81%). Of note, the subcutaneous route of alemtuzumab administration is less effective and is not recommended.[32,33] After dose escalation with appropriate premedication (first week 3-10-30 mg), 30 mg three times a week is maintained until maximal response (maximum of sixteen weeks) or intolerable toxicity. Prophylaxis for Pneumocystis jiroveci and Herpes viruses as well as CMV infection monitoring have to be performed. Purine analogues, and particularly pentostatin, have been studied in the treatment of T-PLL. A retrospective analysis of pentostatin administered in 55 patients showed an ORR of 45% with 9% CR.[34] The association of pentostatin and alemtuzumab was studied in a prospective phase II study in thirteen T-PLL patients. An ORR of 69% and 62% CR with a lot of infectious complications.[35] Therefore, the combination of pentostatin-alemtuzumab should be reserved to obtain a CR in patients with suboptimal response to single agent alemtuzumab or in patients with pleuro-peritoneal effusions or liver infiltration known to be more resistant to the antibody alone.

The best OS and progression free survival (PFS) are observed in patients treated with first line alemtuzumab who achieved a CR. However, the majority will relapse within one year. Therefore, intensification therapy is required whenever it's possible. Allogeneic SCT achieves an OS and PFS of only 0-30% due to a treatment related

toxicity (TRM) up to 40%.[36,37] Autologous SCT led to greater relapse rates than allogeneic SCT but induced less TRM reaching approximately the same OS.[38] Age, donor availability and co-morbidities will guide the physician in the choice of transplantation type and conditioning regimen.

Rechallenge with alemtuzumab may be considered if relapse occurs six months after the first administration and if tumour cells still express CD52. In alemtuzumab refractory patients, purine analogue or bendamustine based regimens are good options.[39,40]

B-cell prolymphocytic leukaemia

Presentation and diagnosis

B cell prolymphocytic leukaemia (B-PLL) is an even more rare neoplasm characterised by mature B cell proliferation in blood, bone marrow and spleen. The definition based on the WHO haematological malignancies classification, includes blood and bone marrow infiltration by more than 55% B prolymphocytes (B-PL). Atypical chronic lymphocytic leukaemia (CLL), CLL with prolymphocytic transformation (less than 55% B-PL mixed with typical CLL lymphocytes), and mantle cell lymphoma with t(11;14) (q13;q32) and cyclin D1 rearrangement are excluded from this entity. However, a recent gene expression profiling and immunophenotyping study suggests that B-PLL could be a heterogenic group of pathologies ranging from a subgroup close to CLL to a subgroup with full overlap with MCL.[41] The disease represents 1% of chronic B cell leukaemias and is predominant in elderly patients (65-70 y) with an equal sex distribution. Rapidly progressive lymphocytosis (with typically more than 90% B-PL in peripheral blood) and massive splenomegaly are the most common features of the disease. Anaemia and thrombocytopenia are present in 65% and 35% of cases, respectively. Lymphadenopathies are not prominent and B symptoms are frequent.

As in T-PLL, diagnosis is based upon clinical presentation, morphology, flow cytometry and genetic assessment. Correct identification of B-PLL may be difficult because of similarities with other B cell malignancies (CLL, MCL, SMZL, and HCL). In B-PLL, peripheral blood shows more than 55% monomorphic B-PLs. These cells have twice the size of a CLL cell, have a nucleus with moderately condensed chromatin and a prominent nucleolus, have more abundant cytoplasm than a normal lymphocyte and show a regular outline. The bone marrow biopsy reveals a nodular or interstitial infiltration without proliferation centres as observed in CLL.[24] Pan B cell markers (CD20, CD22, CD24, FMC7, and CD79b) and surface immunoglobulin (IgM or IgM/IgD) are strongly expressed. Most cases are CD5- and CD23-, although a few cases can express these antigens. CD10, CD11c, CD103, CD25, cyclinD1, and SOX-11 are not expressed. This means that the Catovsky score (CD5+, CD23+, surface immunoglobulin weak, FMC7-, CD79b weak) does not reach more than one, rarely two, and excludes the diagnosis of CLL.[42] Complex karyotypes are common. Deletions of 17p and p53 mutations are present in more than 50% of cases.[43] Del 13q24 is also frequently described.[44] At the molecular level, c-MYC and AKT genes over-expression and p53 downregulation have been identified in gene expression profiling studies.[45]

Treatment

Because of the rarity of the disease, there are few studies on B-PLL treatment. Treatment indications follow the criteria described by the CLL guidelines meaning that only symptomatic patients have to be treated. In patients without p53 mutations/17p deletions, fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine (B)R are recommended whereas in the presence of p53 mutations/17p deletions, alemtuzumab is indicated. Chlorambucil is rarely useful but splenectomy or splenic irradiation may be performed as palliative support. In young and fit patients who achieve CR, SCT has to be considered. New monoclonal anti-CD20 antibodies and inhibitors of BCR signalling may be therapeutic tools but have to be evaluated in this disease.

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Key messages for clinical practice

1. T-LGL and chronic lymphoproliferative disorder of NK cells are mostly indolent disorders. Treatment is necessary in case of symptomatic cytopaenias or non-haematological autoimmune disorders.

2. First line therapy of T-LGL and chronic lymphoproliferative disorder of NK cells is based on three immunosuppressive drugs: MTX, C and CyA. Clinician's choice is guided by co-morbidities and associated autoimmune manifestations.

3. Aggressive NK cell leukaemia is a rare LGL proliferation in western countries. Induction treatment with a L-asparaginase containing regimen followed by allogeneic SCT has the highest chance to obtain prolonged remissions.

4. T-PLL always follows an aggressive course. The optimal treatment strategy should consist of remission induction with alemtuzumab IV followed by autologous or allogeneic SCT whenever possible.

5. Treatment indications for B-PLL follow the criteria described by the CLL guidelines. After induction with FCR, BR in patients lacking a p53 mutation or deletion or alemtuzumab in case of a p53 mutation or deletion, SCT must be considered.

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