CHRONIC LYMPHOCYTIC LEUKEMIA: CURRENT CONCEPTS IN MANAGEMENT

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Chronic Lymphocytic Leukemia (CLL) is defined as occurrence of > 5X109/l lymphocytes in peripheral blood (or 2-3X109/l lymphocytes with surface markers of CLL) [1]. It is the most frequent type of leukemia and affects mainly elderly individuals (40% of all leukemias in this age group), but about a third of patients are less than 60 years of age at diagnosis [1,2]. It is 20-30 times more common in developed world than in developing countries with a median age of patients between 65 and 70 years. Males are effected twice more commonly than females [1].

In our centre it constituted for 6% cases of all haematological malignancies. Median age at presentation was 65 years with 58% of patients above the age of 60 years. Male to female ratio was 4:1. About 55% patients presented with early stage disease (Binet stage A) whereas about 33% presented with advanced stage disease (Binet stage C).

STAGING

In a malignant disorder which primarily effect elderly (>60 years age) and is completely asymptomatic in two third of patients it is always a dilemma when to initiate treatment and with what? For years the gold standard for resolving this issue in CLL has been either Rai or Binet stage of the disease (table-1) [3,4]. These systems define early (Rai 0, Binet A), intermediate (Rai I/II, Binet B) and advanced (Rai III/IV, Binet C) stage disease with median estimated survival times of > 10, 5–7, and 1–3 years, respectively [1]. However, there is heterogeneity in the course of the disease among individual patients within a single stage group. Such as within Binet stage A patients was is recognized a group in whom the disease remains stable for years and their survival without treatment is similar to those of same age group without disease. This is termed 'Smoldering CLL [5] Its characteristics are:

- Hb. >13.0 g/dl
- Lymphocytes <30x109/l
- Minimal or no lymphadenopathy
- Non diffuse pattern of lymphocytic infiltration in bone marrow biopsy
- Lymphocyte doubling time >12 hours

Thus clinical staging systems do not allow prediction of onset and rate of disease progression in an individual patient diagnosed with early stage disease. A misconception that patients seldom die of CLL has also been cleared from observations that patients who do have progression of their CLL predominantly die of complications of the disease, especially from infections. The development of newer prognostic factors has allowed for further discrimination of patients into risk categories. On the basis of these factors patients can be categorized into low risk and high risk groups irrespective of the clinical stage. These are shown in (table-2) [6].

Most important of these is mutation status of VH gene. One can divide B-CLL cases into 2 groups, mutated and unmutated, using an arbitrary limit for variation from germ line V genes (≥ 2% differences from germ line = mutated; < 2% difference = unmutated). The cases in the unmutated group have a much more aggressive course than those in the mutated group [6]. As this

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test is not available in routine clinical laboratories, surrogate markers have been investigated (table-2). At the present time, it appears that ZAP-70 correlates better with Ig V gene mutations and therefore may be a convenient clinical surrogate for V gene mutation status. However these do not correlate fully with VH gene mutation status. Second important marker are the genomic aberrations, which can be identified in about 80% of CLL cases by fluorescence in-situ hybridization (FISH) of interphase cell nuclei ("Interphase-Cytogenetics") with a disease-specific comprehensive probe set. These again identify two distinct subgroups of patients, one with 11q deletion 17 p deletions with resistance to treatment and other with 13q deletion with stable disease [7,8].

THERAPEUTIC MODALITIES

Corticosteroids

Prednisone and other corticosteroids as a single agent have a minimal response rate in CLL, predispose to opportunistic infections, and can accentuate hyperleukocytosis. A controversial indication for steroid alone therapy is in resistant disease. Recommended doses are methyle prednisolone 1 gm/m^2/day for 05 days in monthly cycles or 50-100 mg prednisolone day [1].

Alkylating Agents

Chlorambucil is the oldest and best-known treatment for CLL. It can induce partial remissions (PR) in 60%–70% of previously untreated patients, but no significant complete remissions (CR). Combinations of chlorambucil with prednisone became the benchmark of therapy in CLL. and continued for years [9].

Alkylator/anthracycline combinations such as CVP (cyclophosphamide, vincristine, prednisone) and ChOP (cyclophosphamide, doxorubicin, vincristine, prednisone) are frequently used with similar and perhaps better responses to those seen with chlorambucil, but no change in survival [9].

Purine Analogues

The purine analogues are nucleoside analogues that inhibit DNA polymerase and ribonucleotide reductase thus promoting apoptosis. These include fludarabine, cladribine, pentostatin (deoxycoformycin). Of these, fludarabine has been the most widely tested and used nucleoside analogue in CLL. In controlled clinical trials against chlorambucil, overall response (OR) favored the fludarabine group at 63% (20% CR + 43% PR) versus 37% (4% CR + 33% PR). The median duration of remission and the median progression-free survival (PFS) in the fludarabine group were 25 months and 20 months, respectively, whereas both values were 14 months in the chlorambucil group ($P < 0.001$ for both comparisons). An important observation in all the trials is the higher percentage of CRs seen in the fludarabine treated groups. Fludarabine is well tolerated with major side effects being haematologic and immunologic toxicities [10].

Likewise, there is evidence that cladribine (2-CdA) produces similar responses as fludarabine in both previously treated and untreated populations. Results showed a CR of 45.4% and a PR of 82.5% in the previously untreated group with a median survival of 19.4 months, and a CR of 12.5% and PR of 48.4% in the previously treated group with a median survival of 16.3 months. But fludarabine has been shown to be superior in terms of rate and duration complete remission [7].

Combination of the less myelosuppressive agent pentostatin with chlorambucil and prednisone in one Phase II study of untreated CLL patients noted an overall response rate of 87%, including a 44% complete response rate [11].

It is proven that purine analogues are the most active single group of agents in CLL and should form the building block of subsequent

therapies. Fludarabine has been the most extensively studied agent in previously untreated CLL. Because of higher response rate with prolongation of progression-free survival fludarabine is the purine analogue of choice.

Combinations of fludarabine and cyclophosphamide have been developed and are being increasingly used in treating resistant or progressive disease.

Monoclonal Antibodies

Monoclonal antibodies that have been evaluated in controlled clinical trials and are now in use are Rituximab and Alemtuzumab.

Retuximab is a chimeric anti-CD20 monoclonal antibody, which has less myelosuppression and potential for cellular immune suppression. It down-regulates the anti-apoptotic proteins mcl-1 and XIAP expression in CLL cells in vivo, thus offering enhanced response to fludarabine-based therapy. Response correlates with dose, 75% of patients responding at the highest dose (2250 mg/m^2). While many patients treated with rituximab will respond, these are predominantly partial responses, with the bone marrow being the most difficult compartment to treat adequately [7,11].

Alemtuzumab (Campath-1H) is a humanized anti-CD52 monoclonal antibody that effectively fixes complement and depletes normal lymphocytes and lymphoma cells. CD52 is a 21–28 kD glycopeptide antigen is expressed on normal and leukemic B and T lymphocytes, macrophages and monocytes. The toxicity related to the infusion of the antibody has hampered its early use in patients. An OR of up to 87% is reported. In contrast to rituximab, alemtuzumab has its most pronounced effects in blood and bone marrow, with minimal effect on bulky disease. Many of these Campath-1H-treated patients become PCR negative when treated for MRD. It should be avoided in patients with active infections or who have a contraindication to prolonged immunosuppression [7,11].

Other potential targets for immunotherapy, for which antibodies have been developed include IL-2, IL-4, IL-8, IL-6, TNF-α, IFN-γ, SDF, VEGF, HLA-DR, CD20, CD22, CD23, CD52 and HU1D10. The antibodies can be tagged with radioactive or toxic labels to target cells carrying antigen. Of these an IL-2 receptor ligand immunotoxin, Ontac, and radiolabelled mAbs, zevalin, have entered clinical trials.

Immunotherapy

Cellular vaccines involving the leukemia cell that is modified to enhance its capacity to induce an immune response or dendritic cells pulsed with putative leukemia-associated antigens are under investigation. A Phase II study currently is evaluating the effects of multiple injections of autologous Ad-CD154-transduced CLL B cells [10].

A phase I trial testing the safety and biologic activity of activated T-cell therapy has been initiated at University of California, San Diego with Xcyte Therapies, Inc (Seattle, Wash). For this, the patients undergo leukapheresis to remove mononuclear cells that subsequently are cultured ex vivo with anti-CD3/CD28 microspheres. The cultivated autologous T cells subsequently are reinfused as a single intravenous infusion [10].

Haemopoietic Stem Cell Transplantation

Autologous and allogeneic stem cell transplantation (SCT) are increasingly considered in the management of medically fit patients with active CLL. Patients not attaining a complete remission with initial therapy or having high risk genetic abnormalities [i.e., del (11q22-q23), del (17p13), unmutated somatic V_H gene status, and p53 mutations] should be considered good candidates for early application of this modality on well designed clinical trials. In autologous transplant, the transplant mortality is less than 10% with about 50% of

patients relapsing at 4 years. However, the continuing clinical and molecular relapses observed in all series of autologous SCT in CLL are evidence against the curative potential of the procedure in the majority of patients. Furthermore, genetic risk factors appear to retain their adverse impact after autologous SCT. Nevertheless, the median treatment-free interval of 49 months in the VH unmutated cohort suggested a beneficial effect of autologous SCT for this high-risk population [12].

Allogeneic transplant yields overall survival and event-free survival of 41% and 36.6% at 10 years. About 48% of patients died from procedure-related causes. As compared to autologous SCT the primary therapeutic advantage of allogeneic SCT after dose-reduced conditioning is the graft-versus-leukemia effect, which may offer long-term disease control and eventual cure. Therefore, allogeneic SCT appears to combine the favorable features of low TRM with the activity of the graft-versus-leukemia effect, making this procedure a valid option when aiming at cure for high risk CLL. Non myeloablative conditioning with allogeneic stem cell transplant are under continued evaluation [12].

Radiotherapy

Radiotherapy also plays an important role in treatment of CLL. It may be useful in palliation and debulking when administered to spleen (and/or bulky lymph nodes). A complete haematological remission may be achieved in about 38% of patients [1].

Splenectomy

Splenectomy is indicated in following situations: [1].

- Symptomatic massive splenomegaly (not responding to radiotherapy)
- Hypersplenism causing cytopenias
- Autoimmune cytopenias

Other Modalities [13,14]

Major advances in using sophisticated computerized modeling to predict the chemical structure of small molecules that will inhibit these intracellular targets have occurred and these agents are now entering the clinic.

Flavopiridol is a cyclin dependent kinase (cdk) inhibitor. It induces apoptosis of B cell chronic lymphocytic leukemia and lymphoma cells. It is being tested in clinical trials. However this agent has limited potential as monotherapy in the lymphoid malignancies studied thus far but it has potential in combination with a variety of chemotherapy agents.

Some Proteasome Inhibitors are also under investigation. The proteasome is a large, multicentric protease complex with a pivotal role in cellular protein regulation. In order for a protein to be suitable for degradation, it must first be adorned with ubiquitin. The ubiquitin-proteasome pathway plays a critical role in the degradation of intracellular proteins involved in cell cycle control and tumor growth. NF-κB plays a role in maintaining cell viability through the transcription of inhibitors of apoptosis. NF-κB is activated when the proteasome degrades the inhibitor protein 1κBa resulting in downregulation of multiple gene products. PS-341 is a specific and selective inhibitor of the 26S proteasome. It can block activation of NF-κB, which may induce apoptosis and also make cells more sensitive to a variety of chemotherapy agents.

MANAGEMENT

Diagnosis

Important issues in CLL care can be divided by four junctures met during the course of each patient's disease: [1] making the definitive diagnosis of CLL and determining individual patient prognosis; [2] determining when to treat the CLL; [3] determining how to initially treat the CLL; and determining a salvage regimen suitable for an individual patient's case in relapse [11].

Traditionally CLL is diagnosed when lymphocyte count in peripheral blood is 10X109/l and the blood smear shows >90% small or medium sized cells with scanty cytoplasm and nuclei showing clumped chromatin and indistinct nucleoli along with smear cells. A count of 5X109/l with the characteristic B-CLL pattern (CD5 and CD23 positive, surface immunoglobulin weak, CD79b weak or absent, FMC7 negative). This has been codified by the Royal Marsden group. A score of 4 or 5 is found in almost all true B-CLLs. Recently the lymphocyte count limits have been reduced to 5X109/l and 2-3X109/l respectively [1,3,11].

To differentiate from other B cell malignancies immunophenotyping along with scoring is recommended. The panel of Abs and scoring is shown in (table-3). A score of >3 confirms diagnosis of CLL whereas a score of 1-2 is seen in other B cell malignancies e.g. non-Hodgkin Lymphoma.

Other test which may be performed include a direct antiglobulin test (in all anaemic patients) to exclude immune haemolysis, reticulocyte count, serum immunoglobulin levels, chest X-ray and bone marrow aspiration and trephine biopsy to see the proliferation centres and pattern of infiltration. In addition drug sensitivity pattern can be tested using Octospot [1,3,11].

Staging

Next step is to stage the disease. Clinical staging must be performed on all cases. Both Rai and Binet systems can be used but the later is simpler and directly divides the disease into low (stage A), intermediate (stage B) and high (stage-C) risk groups. The systems are shown in (table-1).

If facilities are available then all stage A (also stage B) patients should be tested for other disease burden and activity markers shown in (table-2).

Initiation of treatment

Next comes the decision that whether to start treatment and if so with what. The decision of when to initiate treatment and what type of therapy to initiate with a CLL patient is not straightforward. Currently the decision to treat patients is based on multiple factors including advanced clinical staging, symptomatic disease, burden of disease, age, co-morbid illnesses, adverse prognostic factors, and availability of treatments that alter survival [7]. At initial presentation, the great majority (80-90%) of patients with CLL will be asymptomatic. CLL is generally a disease of the elderly, with a median age at diagnosis exceeding 60 years. Only 10% of patients diagnosed with CLL are under the age of 50 and 1-2% are younger than 40. The stage distribution of patients at diagnosis is similar between younger and elderly patients. only patients with smoldering CLL appear relatively unaffected by their disease, with a 94% 12-year survival in one series and an 85% 14-year predicted survival. A consensus has arisen that early stage B-CLL should not be treated with chemotherapy; rather, watchful waiting should be employed irrespective of the age. An NCI sponsored Working Group on CLL has established guidelines for initiation of treatment [15]. These are as under:

- Progressive marrow failure indicated by development or worsening of anaemia and/or thrombocytopenia.
- Massive (>10 cm) or progressive lymphadenopathy.
- Massive (>6 cm) or massive splenomegaly.
- More than 50% increase in lymphocyte count over 2 months or lymphocyte doubling time <6 months.
- B symptoms
- Autoimmune cytopenias

Treatment [1,7,10,15]

Once it is decided to treat a particular patient then next question will be what agent(s) is to be used in treatment. Chlorambucil is the oldest and best-known treatment for CLL. It can induce partial

remissions (PR) in 60%–70% of previously untreated patients, but no significant (only 4-10%) complete remissions (CR). As a routine it is either administered as a continuous regimen, 0.1 mg/kg body weight (BW) daily, or as intermittent regimen, 0.4 mg/kg BW every 2 weeks. Most promising regimen is a high-dose regimen comprising a fixed 15 mg daily dose of chlorambucil administered until toxicity or complete remission. After attainment of CR, patients are administered a twice-weekly dose of 15 mg of chlorambucil for 3 years. This yielded a higher CR rate (70%) and higher overall survival.

It can be used either alone or combined with corticosteroids (30 mg/day) with marginal improvement in OS.

Cyclophosphamide is another alkylating agent used to initiate therapy in CLL. This can also be administered in a continuous regimen, 2-3 mg/kg BW/day or intermittent regimen, 20 mg/kg once every 2-3 weeks. However it is most often used in combination chemotherapy for advanced stage disease.

Alkylator/anthracycline combinations such as CVP (cyclophosphamide, vincristine, prednisone) and ChOP (cyclophosphamide, doxorubicin, vincristine, prednisone) are frequently used with similar and perhaps better responses to those seen with chlorambucil, but no change in survival. (1) There is no advantage of CVP over chlorambucil in stage B patients, but in Binet stage C CHOP with reduced dose of doxorubicin (mini-CHOP) is associated with a superior outcome. By and large no definite superiority of combination-based approaches over chlorambucil regimens with respect to prolongation of survival has been demonstrated. [11].

Single agent studies with fludarabine have demonstrated a higher complete response rate and overall response rate compared with historical experience with alkylator based regimens. It is administered in daily dose of 25-30mg/m^2 by continuous infusion for 5 days in monthly cycles. In previously treated patients overall response rate is 45% with CR in 3-20% patients. In untreated patients these figures are 70% and 20-40%. Median duration of remission is 25 months and progression free survival is 20 months [4]. Its use as first line therapy is hampered by its cost and side effects (myelosuppression and infections). The response to therapy may be different in genetic subgroups. In particular, the deletion 17p- and/or abnormalities of the p53 gene involved in this aberration have been associated with failure after treatment with alkylating agents, purine analogs and also rituximab. Alemtuzumab may be effective in CLL with 17p-/p53 mutation (1) It is thus important to assess the response objectively. NCI working group has developed criteria to assess response to any therapy. These are listed in (table-4) [1,7,10,11,15].

Cladribine, another purine analogue, can also be used in place of fludarabine. It is used in doses of 0.1 mg/kg BW/day by continuous IV infusion for 7 days in monthly cycles. Alternatively it can be administered over 2 hours in doses of 0.12-0.14 mg/kg BW/ day for 5 days. It can also be used orally in doses of 10 mg daily for 5 days. In previously treated patients overall response rates of 48-72% and CR of 4-39% are reported. In untreated patients these figures are 80% and 10-45% with a median survival of 19.4 and 16.3 months respectively. However it is more myelosuppressive than fludarabine.

Purine analogues can be combined with alkylating agents if patient is resistant to monotherapy with either of these. The definition for fludarabine-refractory disease is no response to therapy or initial response to fludarabine but subsequent progression within a 6-month period from completion of therapy. Fludarabine is combined with cyclophosphamide in a cyclical administration (fludarabine 30 mg/dayX03 + cyclophosphamide 300-500 mg/m^2/dayX3. Overall response rate in patients resistant to monotherapy is 38%. If used as first line therapy, the response rate is > 80% with 35%

CR. However, the estimated median survival is 12 months for those patients who were fludarabine-refractory. Significant infections are seen in 48% of fludarabine-refractory patients compared with 18% of patients not refractory to fludarabine.

Combination of the less myelosuppressive agent pentostatin with chlorambucil and prednisone in one study of untreated CLL patients noted an overall response rate of 87%, including a 44% complete response rate.

Monoclonal antibodies (rituximab and alemtuzumab) are seldom used as first line therapy or as monotherapy. In trials retuximab in doses of 375 mg/m^2 IV weekly for 4 weeks yielded only 13% response rate. In increased doses up to 45% response rate can be achieved. It however causes severe allergic reactions. Responses are slightly better with alemtuzumab (33-53%) in dose of 30 mg IV 3 times a week for up to 16 weeks. In p53 abnormal CLL it yields better results.

Fludarabine and cyclophosphamide have been combined with rituximab in the FCR regimen with fludarabine being given at 25 mg/m^2/day for 3 days, days 1 to 3, and cyclophosphamide 250 mg/m^2 3 times a day. Rituximab is given at a dose of 375–500 mg/m^2 on day 1. The overall response rate is 95% with 69% complete remission rate. Of interest, 82% of the CR patients have a CD5 + lymphocytes percentage in the bone marrow of < 1%. In addition, approximately half of the patients are able to become PCR negative for the IgVH gene. In fludarabine resistant patients 73% of patients responded with 25% attaining a CR. fludarabine-refractory disease, a 5% complete response rate and 59% overall response was observed.

The combination of fludarabine and alemtuzumab yield an OR rate of 92%. CMV infection is the major complication.

RECOMMENDATIONS

Treatment of Early Stage Disease

Treatment of early stage disease (Binet stage A, Rai stage O) is not recommended.

Treatment of Progressive or Advanced Stage Disease

When signs of progression appear or patient presents in advanced stage disease (Binet stage B & C, Rai stage I-III) following options are available:

- Fludarabine + cyclophosphamide / chlorambucil (MRC CLL4)
- If fludarabine is contraindicated (autoimmune cytopenia, severe renal impairment) or a palliative approach is contemplated the treatment should be started with chlorambucil in usual doses.
- If patient is fit for allogeneic transplant then after remission with one of above, it should be considered.

Monoclonal antibodies are not recommended as initial therapy.

Treatment of Relapse

If patient relapses after initial response, following options may be considered:

- In patients who relapse after response to low dose chlorambucil, the same should be re-employed.
- If patient is refractory to chlorambucil and fludarabine is not contraindicated then therapy may be started with fludarabine.
- If fludarabine is contraindicated CHOP or COP may be considered.
- If patient who responded to fludarabine bur relapses after one year, fludarabine may be administered again.
- If patient relapses within one year of fludarabine therapy then fludarabine+cyclophosphamide should be considered.
- In more aggressive disease (or p53 gene abnormalities) combination of fludarabine, cyclophosphamide and a monoclonal antibody may be considered.

Table-1: Clinical staging of CLL.

System	Clinical stage	Features	Patients
Binet et al	A	<3/5 lymphoid areas (cervical, axillary, inguinal, liver, spleen)	60%
	B	>3/5 lymphoid areas	30%
	C	Hb <10.0 g/dl and/or platelet count <100x10^9/l	10%
Rai et al	O	Lymphocytosis only	30%
	I	Lymphadenopathy	25%
	II	Hepatosplenomegaly+ Lymphadenopathy	25%
	III	Hb. <11.0 g/dl	10%
	IV	Platelet count <100x10^9/l	10-%

Table-2: Risk stratification based on additional markers.

Group	Marker	Cut-off value	Low risk	High risk
Tumour burden/activity	Lymphocyte count (X10^9/l}	7.5	<7.5	>7.5
	Bone marrow infiltration pattern		Non-diffuse	Diffuse
	Serum LDH			
	Lymphocyte doubling time		<12 months	>12 months
Serum markers	Thymidine kinase (U/l)	7.1	<7.1	>7.1
	β2- microglobulin			
	Soluble CD23			
Genetic markers	Chromosomal abnormalities		13q-, +12q	17p-, 11q-
	VH mutations	2% from germ line	≥2%Mutated	<2% Mutated
	p53		Normal	Lost or mutated
Surrogate markers for VH	ZAP 70		Not expressed	Expressed
	CD38		Expressed	Not expressed
	LPL			

Table-3: Immunodiagnosis of CLL.

Marker	Score 1	Score 0
SmIgG	Weak	Strong
CD5	+	-
CD23	+	-
FMC7	-	+
CD22 or CD79b	Weak	Strong

Table-4: Response criteria in CLL.

Criteria	Complete response (CR)	Partial response (PR)	Progressive disease
Symptoms	None	-	-
Lymph nodes	None	>50% decrease	>50% increase or new nodes
Liver/spleen	Not palpable	>50% decrease	>50% increase
Hb (g/dl) (untransfused)	>11.0	>11.00 or >50% improvement from base line	-
Neutrophils (X10^9/l)	>1.5	>1.5 or >50% improvement from the base line	-
Lymphocytes (X10^9/l)	<4.0	>50% decrease from the base line	>50% increase from the base line
Platelets (X10^9/l)	>100	>100 or >50% improvement from the base line	-
Marrow aspirate	<30% lymphocytes	-	-
Marrow trephine biopsy	No interstitial or nodular infiltrate	May be residual lymphoid nodules	-

Treatment of Refractory Disease

If disease does not respond to treatment or progresses then following options are to be considered:

- In patients with bulky disease and p53 abnormalities, high dose methyl prednisolone is recommended.
- In patients without bulky disease and with p53 abnormalities and those who are resistant to fludarabine alemtuzumab is recommended.
- Autologous stem cell transplantation should be considered, but in a controlled trial (MRC CLL5).
- Allogeneic stem cell transplantation should be considered if patient is other wise fit.

COMPLICATIONS

Autoimmune Cytopenias

Autoimmune cytopenias, particularly haemolytic anaemia may be present at presentation, may appear during disease progression or result from fludarabine treatment. These are treated as otherwise, with steroids with or without cyclosporine A. Retuximab may be useful in treatment of AIHA [1].

Infections

Infections are common in CLL both treated and untreated. These can be bacterial, parasitic or viral. If patient has hypogammaglobulinaemia then IVIG at a dose of 400mg/kg every three weeks for one year may be administered prophylactic ally. If patient is severely neutropenic use of G-CSF is recommended to prevent infections [1].

Patients receiving purine analogues and/or monoclonal antibodies should be given prophylaxis against bacterial, viral and pneumocystis infection.

Infections appearing during the course of disease or treatment should be investigated properly and appropriate chemotherapeutic agents should be administered.

Lymphomatous Transformation

Richter lymphomatous transformation occurs in 5-10% of patients at any time during the course of disease. These are treated as in case of de novo lymphomas. No standard treatment is recommended. [1].

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