Hong Kong J Radiol. 2011;14(Suppl):S56-62

REVIEW ARTICLE

Management of Chronic Lymphocytic Leukaemia

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ABSTRACT

Chronic lymphocytic leukaemia is a disease that primarily affects the elderly and has a heterogeneous clinical course. The past decade has witnessed extensive progress in its management, owing to the generation of prognostic biological markers that influence therapeutic decisions, as well as the development of novel therapeutic agents that improve the treatment response and survival. This review discusses the value of various prognostic markers in the management of chronic lymphocytic leukaemia and the treatment options with conventional chemotherapy and newer chemoimmunotherapy regimens. However, treatment needs to be tailored to individual patients according to the patient's general physical state, ability to tolerate treatment-related toxicity, and presence of comorbidities. To that end, an approach to formulating primary and secondary treatment decisions is also presented.

Key Words: *Combined Modality Therapy; Leukemia, lymphoid; Lymph nodes; Rituximab*

中文摘要

慢性淋巴細胞白血病的治療

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慢性淋巴細胞白血病具臨床異質性，患者多為老年人。過去十年間對於慢性淋巴細胞白血病的治療方法有廣泛進展，不但發現了使用預後性生物標記物來影響治療對策，還發明了新的藥物以改善患者的治療反應及生存期。本文討論不同的預後標記物在治療慢性淋巴細胞白血病中的價值，以及使用傳統化療及新的免疫化療的治療選擇。然而，不同的患者都須要根據其身體狀況、對治療引致的毒性的容忍度、及其共病作出針對性的治療方案。為此，本文會提出制定初次及再次治療的決定。

INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia in the western world. While Australia and the US have the highest incidence, the incidence in Hong Kong is nearly 10 times lower than in the US.[1,2] Moreover, CLL primarily affects the elderly; almost 70% of patients are older than 65 years at the time of diagnosis, and less than 2% are younger than 45 years.[1,3]

CLL is not a curable disease and therefore the goal of therapy is to maintain the best quality of life and keep patients symptom-free. The disease has a heterogeneous clinical course, with some patients living

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for decades without treatment, while others show a rapidly progressive clinical course.[3] A wide range of effective therapies is now available for treatment-naïve as well as relapsed and refractory CLL. This review discusses the recent approach to the management of CLL with chemotherapy and rituximab-based chemoimmunotherapy regimens.

DIAGNOSIS OF CHRONIC LYMPHOCYTIC LEUKAEMIA

CLL is a mature B-cell neoplasm, characterised by the presence of more than 5 x 10^9 /L of clonal B lymphocytes in the circulation. Morphologically, its cells are small lymphocytes with scanty, agranular cytoplasm and round nuclei with condensed chromatin.

Immunophenotypically, CLL cells are positive for CD5, CD19, CD20, and CD23, but negative for FMC-7. Compared with normal B cells, CLL cells express lower levels of surface immunoglobulins (IgM and IgD), CD20 and CD79b.[4,5] CLL should be distinguished from other lymphoproliferative disorders such as follicular lymphoma and mantle cell lymphoma, in view of the different prognosis and management strategies for the latter conditions.

CLINICAL STAGING

The staging systems widely used in CLL include the Rai and Binet systems.[6,7] Both systems are simple and rely solely on physical examination and standard laboratory tests.[8]

Rai Staging

This clinical staging system depends on grading based on increasing clinical and laboratory evidence of the disease (Table 1).[6]

Binet Staging

This is a classification depending on three prognostic groups based on the extensiveness of lymphadenopathy, involvement of the liver and spleen, and the presence of anaemia and/or thrombocytopenia (Table 2).[7]

Table 1. Rai staging system of chronic lymphocytic leukaemia.[6]

Stage	Symptoms
0	Lymphocytosis only
I	Lymphocytosis with lymphadenopathy
II	Lymphocytosis with splenomegaly and/or hepatomegaly
III	Lymphocytosis with anaemia (Hb <110 g/L)
IV	Lymphocytosis with thrombocytopenia (platelet count <100 x 10^9 /L)

Abbreviation: Hb = haemoglobin.

Table 2. Binet staging system of chronic lymphocytic leukaemia.[7]

Stage	Symptoms
A	No anaemia, no thrombocytopenia; <3 involved areas
B	No anaemia, no thrombocytopenia; ≥3 involved areas (including axillary, cervical, inguinal, lymph nodes, whether unilateral or bilateral, spleen and liver)
C	Anaemia (Hb <100 g/L) and/or thrombocytopenia (platelet count <100 x 10^9 /L), independent of lymphadenopathy or organomegaly

Abbreviation: Hb = haemoglobin.

PROGNOSTIC FACTORS

Considering the heterogeneous clinical course of CLL, various prognostic factors are employed to predict disease progression and stratify patients for treatment. In addition to the clinical stage, other parameters that affect prognosis have also been identified.[9]

Molecular Cytogenetics

Cytogenetic aberrations, identified in more than 80% of CLL cases using fluorescence in-situ hybridisation, provide prognostic information.[10] The common chromosomal aberrations in CLL include deletions in chromosome 13 [del(13q)], chromosome 11 [del(11q)], chromosome 17 [del(17p)], and trisomy of chromosome 12. Studies have indicated that patients with CLL cells showing del(11q) or del(17p) have outcomes that are inferior to persons with leukaemic cells with normal karyotype or del(13q) as the sole genetic abnormality.[10] Furthermore, the presence of del(17p) is the strongest predictor of poor treatment outcomes and survival.[10] Similarly, presence of the *p53* gene mutation is also associated with a poor prognosis.[11]

Mutational Status of IgV_H and Expression of ZAP-70 or CD38

Expression of CD38 and ZAP-70 in CLL cells (as assessed by fluorescence-activated flow cytometry analysis) influences the overall prognosis. Various studies have shown that CLL patients with high CD38 or ZAP-70 expression have poor survival.[12-15] Furthermore, the status of somatic mutations in the immunoglobulin heavy chain variable region gene (IgV_H) as well as a particular IgV_H gene have also been shown to predict disease outcome; patients with unmutated IgV_H have a worse clinical outcome than those in whom it is mutated.[12,16] Although expression profiling has demonstrated that ZAP-70 is differentially expressed in CLL with unmutated IgV_H, the association between its expression and unmutated IgV_H status is not absolute. Hence, ZAP-70 expression cannot be regarded as a perfect surrogate for IgV_H mutation status.[8]

Serum Markers

Serum markers (including CD23, thymidine kinase and β_2-microglobulin) may be useful for predicting overall survival (OS) or progression-free survival (PFS).[17-20]

Bone Marrow Examination

Bone marrow biopsy is not necessary to make a diagnosis of CLL. However, in patients presenting with anaemia and thrombocytopenia, a marrow biopsy helps to evaluate whether the cytopenias are immune-mediated or due to heavy marrow infiltration.[3] A predominantly diffuse pattern of infiltration of bone marrow by CLL cells has been shown to be associated with a poor disease prognosis.[3,8]

Lymphocyte Doubling Time

Lymphocyte doubling time, defined as the period needed to double the peripheral blood lymphocyte count, is a simple and valid parameter to assess disease progression and monitor early stage disease. Lymphocyte doubling time of less than 12 months predicts an aggressive course and short survival, while a longer doubling time and stable lymphocyte counts are associated with an indolent disease course.[21]

Age and Comorbidity

Advanced age (>65 years) is considered a poor prognosticator for CLL.[1,3] Given that CLL is common in the elderly, assessment of each patient's physical status is recommended, as survival is significantly impaired in those with multiple and/or severe comorbidities.[22] Although age per se does not determine when a patient should receive treatment, it affects treatment decisions as comorbidities associated with increased age may limit the tolerance to chemotherapy-related toxicity.

TREATMENT OPTIONS

First-line Treatment

Monotherapy

The armamentarium for CLL therapies includes various conventional chemotherapeutic agents and, more recently, monoclonal antibodies which may be used as monotherapies or combination therapies to enhance treatment efficacy (Table 3).[23] While the alkylating agent chlorambucil was the mainstay of CLL treatment in the past, newer agents such as fludarabine and bendamustine have demonstrated better efficacy in terms of complete remission (CR), overall response (OR) and PFS.[24-26]

Table 3. Standard drugs used in the treatment of chronic lymphocytic leukaemia.[23]

Stage	Symptoms
Chlorambucil	Alkylating agent
Fludarabine	Purine analogue
Cyclophosphamide	Alkylating agent
Bendamustine	Alkylating agent
Alemtuzumab	Monoclonal anti-CD52 antibody
Rituximab	Monoclonal anti-CD20 antibody

In a German study, however, first-line fludarabine did not confer any survival benefit over chlorambucil among CLL patients older than 65 years.[27] In the latter study, although fludarabine treatment was significantly superior to chlorambucil in terms of OR (72% vs 51%; p=0.003), CR (7% vs 0%; p=0.011), and time-to-treatment failure (11 vs 18 months; p=0.004), there was no difference in PFS (19 vs 18 months; p=0.7) and OS was shorter with fludarabine (46 vs 64 months; p=0.15).[27]

In addition to chemotherapy, the anti-CD52 monoclonal antibody alemtuzumab has demonstrated efficacy in CLL as a single agent. Hillmen et al[25] demonstrated that single-agent alemtuzumab significantly improved PFS (42% reduction in the risk of progression or death; hazard ratio [HR]=0.58; p=0.0001), time-to-alternative treatment (23.3 vs 14.7 months; HR=0.54; p=0.0001), OR (83% vs 55%; p<0.0001), and CR (24% vs 2%; p<0.0001) compared to chlorambucil as first-line treatment for CLL. Notably, the therapy also seems to benefit CLL patients with the poor cytogenetic risk factor del(17p).[25]

Combination Chemotherapy

The superiority of combination chemotherapy with fludarabine plus cyclophosphamide (FC) over fludarabine monotherapy was demonstrated in three randomised controlled trials.[28-30] In the CLL4 study conducted by UK researchers, the use of the FC combination was associated with a better CR rate (38%) than fludarabine (15%) or chlorambucil (7%) monotherapy. Five-year PFS was also significantly better with FC (36%) than fludarabine (10%) or chlorambucil (10%; p<0.00005). However, the FC combination was more toxic; patients were more prone to develop neutropenia and had longer hospital stays.[28]

The US Intergroup Trial E2997 also showed that first-line treatment using the FC combination was significantly better than fludarabine alone in terms of CR (23.4% vs 4.6%; p<0.001), OR (74.3% vs 59.5%,

p=0.013), and PFS (31.6 vs 19.2 months, p<0.0001).[29] As expected, FC was associated with more toxicity, particularly thrombocytopenia and anaemia.[29]

The efficacy of FC was also demonstrated in previously untreated CLL patients with advanced disease who were younger than 66 years. In the German CLL study, FC was associated with significantly better CR (24%) and OR (94%) than fludarabine alone (7% and 83%; p<0.001 and p=0.001).[30] The better response also translated into significantly longer median PFS (48 vs 20 months; p=0.001) and treatment-free survival (37 vs 25 months; p<0.001). Once again, the use of FC was associated with greater haematological toxicity.[30]

Rituximab-based Chemoimmunotherapy

Although the anti-CD20 monoclonal antibody rituximab alone has only modest efficacy in CLL, its addition to fludarabine-based chemotherapy regimens (chemoimmunotherapy) is an effective therapy for chemotherapy-naïve CLL patients. While many studies have investigated the efficacy of rituximab plus fludarabine-based chemotherapy, novel combinations involving rituximab with pentostatin and mitoxantrone have also been studied.

In an open-label phase II study at the MD Anderson Cancer Centre, 300 treatment-naïve CLL patients with symptomatic or progressive disease were treated with six cycles of chemoimmunotherapy comprising of fludarabine, cyclophosphasmide and rituximab (FCR). After a median follow-up of six years, the overall response rate (ORR) was 95% and CR rate was 72%. Six-year overall and failure-free survival rates were 77% and 51%, respectively. Median time-to-progression was 80 months. Compared with a historical cohort of CLL patients treated in the same institution with fludarabine alone or FC or mitoxantrone, the FCR regimen was superior and associated with improved survival.[31]

The efficacy of FCR was further confirmed in a phase III randomised controlled trial by the German CLL Study Group, in which 817 treatment-naïve CLL patients were randomly assigned to receive six courses of FC or FCR. Patients receiving FCR showed significantly better CR rates (44% vs 22%) and ORR (90% vs 80%; both p<0.0001) compared to FC recipients. The respective PFS and OS at three years in the FCR group were 65% and 87% compared to 45% and 83% in the FC group (HR=0.56; p<0.0001 for PFS; HR=0.67; p=0.01 for OS).[32] However, addition of rituximab to FC did not confer any OS advantage to patients with del(17p). FCR appeared to be more toxic than FC, and resulted in a higher rate of grade 3-4 neutropenia and leucocytopenia which were not associated with an increased rate of infection. Overall treatment-related mortality was similar in the two groups (2% in FCR group vs 3% in FC group).[32]

In an attempt to improve treatment efficacy, modifications of the original FCR regimen have been evaluated. A phase II study showed that the addition of mitoxantrone to FCR (R-FCM) was well-tolerated and effective in previously untreated CLL, and associated with an OR rate of 93% and CR rate of 86%.[33] Patients with del(17P) did not perform as well, with the CR being 25%. Another study with R-FCM by the MD Anderson Cancer Centre also showed similar results.[34] Thus, compared to the original FCR regimen, R-FCM did not seem to confer an additional benefit.

Although FCR is an effective first-line therapy for CLL, treatment-related toxicity is still a major concern, especially in elderly patients. To improve safety while maintaining efficacy, a less-intensive regimen known as FCR-Lite, using smaller doses of fludarabine and cyclophosphamide than in the original FCR regimen, has been evaluated. In a single-arm study with 50 untreated CLL patients who received FCR-Lite , the ORR and CR rates were 100% and 79%, respectively, and the CR was durable. Grade 3-4 neutropenia was markedly reduced compared to the original FCR regimen.[35] A larger trial is warranted to confirm these results.

Second-line Treatment (for Relapsed or Refractory Disease)

Despite the use of effective chemoimmunotherapies, some CLL patients do not respond to treatment or become refractory to fludarabine.[36] Factors that influence the management decision include individual patient characteristics, prior therapy, and response to prior therapy.[37] Generally, using the same first-line treatment regimen is effective for CLL that relapses after two years (late relapse). However, for primary refractory or early relapsed CLL, very limited therapeutic options are available.[23]

Alemtuzumab

The anti-CD52 monoclonal antibody alemtuzumab is an effective agent in fludarabine-refractory CLL. As monotherapy, alemtuzumab induces an OR in about

30 to 40% of patients with fludarabine-refractory CLL. Nevertheless, the responses are not durable and median survival is approximately 1 to 2 years.[36] Alemtuzumab may be combined with fludarabine, cyclophosphamide, and/or rituximab, and other agents such as lenalidomide to improve the survival of fludarabine-refractory CLL.[36]

Rituximab

Patients with relapsed CLL that is sensitive to fludarabine or fludarabine-naïve may be treated with FCR. The REACH (Rituximab in the Study of Relapsed Chronic Lymphocytic Leukaemia) study showed that FCR improved patient outcomes compared with FC. Treatment with FCR resulted in significantly better OR and CR rates compared to FC (70% vs 58% and 24% vs 13%, respectively). After a median follow-up of 25 months, patients receiving FCR also showed significant improvement in PFS (median, 30.6 vs 20.6 months; $p<0.001$).[38]

In addition to fludarabine-based regimens, bendamustine and rituximab combination chemoimmunotherapy (BR) has also been evaluated in relapsed or refractory CLL. In a multicentre phase II study that recruited 78 patients with relapsed and/or refractory CLL, an OR rate of 59% and a CR rate of 9% were obtained after six cycles of BR. In fludarabine-refractory patients (n=22), the OR rate was 46% but no patient had CR.[39] After a median follow-up of 24 months, the median event-free survival was 15 months.[39]

Ofatumumab

Ofatumumab is a novel anti-CD20 monoclonal antibody recently approved by the US Food and Drug Administration for the treatment of CLL resistant to both fludarabine and alemtuzumab. In early clinical trials, ofatumumab demonstrated single-agent activity against CLL and B-cell non-Hodgkin's lymphoma.[40] The interim analysis of an ongoing study in fludarabine- and alemtuzumab-refractory (FA-ref) CLL patients and fludarabine-refractory CLL patients with bulky (>5 cm) lymphadenopathy (BF-ref) showed that ofatumumab therapy conferred clinical improvements.[41] The ORRs were 58% and 47% in the FA-ref and BF-ref groups, respectively. However, the responses were not durable and the median PFS was 5.7 months in the FA-ref group and 5.9 months in the BF-ref group. OS in the FA-ref and BF-ref groups were 13.7 months and 15.4 months, respectively. Ofatumumab was generally well-tolerated with only a small percentage of patients developing grade 3-4 neutropenia and infections. Ofatumumab treatment was also associated with infusion reactions that were observed in approximately 60% of patients.[41]

Haematopoietic Stem Cell Transplantation

CLL is not a curable disease by chemotherapy, and allogeneic haematopoietic stem cell transplantation (HSCT) is the only treatment modality that might offer a cure. Since most CLL patients are elderly, HSCT is not an appropriate treatment option for the majority. According to the European Group for Blood and Marrow Transplantation guidelines, allogeneic HSCT is a reasonable option for eligible patients showing non-response or early relapse (within 12 months) after purine analogue therapy, relapse within 24 months of achieving a response with first-line chemoimmunotherapy or autologous HSCT, and with *p53* abnormalities. Early referral to transplant centres is recommended for these patients, so as to avoid excessive cytotoxic pretreatment and disease transformation.[42]

PATIENT SELECTION FOR CHRONIC LYMPHOCYTIC LEUKAEMIA TREATMENT

Newly diagnosed patients with asymptomatic, early stage disease (Binet stage A) do not require any treatment. A 'watch-and-wait' approach is followed whereby patients are monitored without therapy unless there is evidence of disease progression as defined by the International Workshop on Chronic Lymphocytic leukaemia.[8,9] Various studies have shown that the use of alkylating agents in patients with early stage disease does not prolong survival.[43-45] Patients with Binet stage B or C, on the other hand, benefited from therapy.[8]

The decision to initiate therapy should be based on clinical staging as well as assessment of physical fitness, comorbidities, and prognostic factors. Patients with symptomatic, advanced disease who are young, physically fit and with no major comorbidities may be considered for FCR. Elderly patients who are physically unfit and with serious comorbidities may receive chlorambucil with or without rituximab.[9] Other patients who do not fall into these two categories may be offered a less intensive treatment regimen such as FCR-Lite and BR. CLL patients with del(17p) or *p53* mutations should be treated with first-line alemtuzumab, as they are unlikely to respond to conventional fludarabine-based chemotherapy.[9,46]

CONCLUSION

CLL has a heterogeneous clinical course and is

predominantly a disease of the elderly. The decision to treat the condition should be based on clinical staging, presence of symptoms, disease activity, and the physical fitness of individual patients. In the past decade, novel combination therapies such as chemoimmunotherapy combinations have demonstrated significant efficacy in terms of improved response rates and treatment-free survival in treatment-naïve patients. Recent data have confirmed that rituximab-based chemoimmunotherapies induce high response rates in previously untreated CLL patients and in those with relapsed and fludarabine-resistant disease. Alemtuzumab and ofatumumab also have a role in patients with relapsed and refractory CLL.

ACKNOWLEDGEMENTS

We would like to thank Dr Pradnya Kulkarni from UBM Medica for editorial support. Funding for the editorial support was provided by Roche. We do not have any conflicts of interest to declare.

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