Recent Advances in the Management of Chronic Lymphocytic Leukaemia

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Epidemiology

Chronic lymphocytic leukaemia (CLL) is a rare neoplasm, but is the commonest adult leukaemia in the western population accounting for 24% to 38% of all leukaemias. Among Chinese, according to two hospital-based series, it constitutes 12.5% and 4.6% of all leukaemias in Hong Kong and Beijing respectively. Annual incidence rates of CLL reported in the 1990s were 2.3 to 4.5 per million in the western countries, 0.5 per million in China Mainland, and 0.15 per million in Hong Kong. Similarly low incidence rates of CLL were also reported among other Asian races like Japan, Korea and India. Current data attribute such racial variations in incidence pattern of CLL to familial or genetic rather than environmental factors.

Demographic features

In all populations, the majority of CLL patients are above 50 years of age at the time of presentation, with a median age between 65 and 70 years, and a male to female ratio of approximately 2:1. Pooled data from three local studies showed 93% of 103 Chinese patients with CLL were above the age of 50 at the time of diagnosis and the male to female ratio was 1.5:1.

Diagnosis

Patients with CLL may present with symptoms of anaemia, lymphadenopathy, or systemic symptoms of malaise and weight loss. In the present era, an increasing number of patients are being diagnosed as an incidental finding of lymphocytosis on routine blood test. A definitive diagnosis requires the combination of (i) a peripheral lymphocytosis, (ii) characteristic lymphocyte morphology, and (iii) characteristic immunophenotype. The WHO recommends a persistent lymphocyte count > 10 x 10^9/L for the diagnosis of CLL, but a diagnosis with lymphocyte count < 10 x 10^9/L is possible provided the morphology and immunophenotype are typical of CLL. According to most international guidelines formulated in the recent decade - the US National Cancer Institute, the UK CLL Working Group, the Italian Society of Haematology, an absolute lymphocytosis with a lower limit of > 5 x 10^9/L is required for the diagnosis of CLL. The morphology of typical CLL cells is one of mature, small or medium sized lymphocyte with clumped chromatin, indistinct or absent nucleoli, and scanty cytoplasm. The variant CLL with increased prolymphocytes (CLL/PL) is defined by >10% but <55% prolymphocytes. Immunophenotypes can be demonstrated by means of flow cytometry or by a panel of monoclonal antibodies, and immunophenotyping should be performed in all cases especially those requiring treatment. Typical CLL lymphocytes should co-express CD5, CD19, CD23, together with kappal or lambda light chain restriction, a low density of surface immunoglobulin (SmIg), and a weak CD20. Following the introduction of the WHO classification, only B-CLL exists. The disease entity T-CLL no longer exists but appears as variant T-cell chronic prolymphocytic leukaemia (T-PLL) or T-cell large granular lymphocyte leukaemia (T-LGL). With the demonstration of monoclonality of lymphocytes in the peripheral blood, most centres now consider marrow examination not essential for the diagnosis of CLL. Nonetheless, marrow examination is valuable for providing diagnostic information in atypical cases as well as for providing prognostic information. A greater than 30% lymphocytes in the marrow is consistent with the diagnosis of CLL. Likewise lymph node biopsy is not necessary in the initial diagnostic workup of CLL, but may be indicated when the diagnosis is uncertain, or in patients who develop bulky lymphadenopathy where biopsy may help to exclude transformation to large cell lymphoma (Richter’s transformation of CLL) which may occur in up to 5% of CLL patients.

Prognostic Stratification

With the advancement of medical technology, diagnostic workup of many diseases is nowadays coupled with identification of prognostic factors. The clinical staging systems developed by Binet in 1981 and Rai in 1975 (Table 1) are still widely used and remain the cornerstone in risk stratification of CLL patients. They are easy to apply and well-validated, but do not accurately segregate patients with a rapid disease progression from those with an indolent course. Other prognostic factors that are independent of the clinical stage can now help to refine the outcome prediction. These include patient’s gender (poorer outcome in male), serum LDH, lymphocyte doubling time, pattern of marrow infiltration, and serum β2-microglobulin (β2M). Newer biological markers comprise interphase cytogenetics by fluorescence in situ hybridisation (FISH), CD38 positivity, mutational status of immunoglobulin heavy chain variable region (IgVH), and cytoplasmic expression of zeta-associated protein (ZAP-70) which correlates with lack of IgVH gene mutation. High-risk features for CLL include Rai stage III/IV or Binet stage C; elevated serum β2M; CD38 expression in >30% of lymphocytes; ZAP-
Treatment

In the past, treatment of CLL was of palliative intent. With the availability of highly effective and potentially curative treatment modalities, and the establishment of reliable patient risk stratification algorithms, individualised patient care is now possible. Treatment modalities for CLL in the 21st century include purine analogues, immunotherapy/chemo-immunotherapy, and nonmyeloablative stem cell transplantation.

According to most guidelines11,12,13, treatment for CLL patients should be considered if they have CLL related symptoms, or progressive lymphocytosis with an increase of >50% over a two-month period, or immune anaemia / thrombocytopenia responding poorly to corticosteroid therapy. This includes most of the Binet stage B and C patients, and some of the stage A patients with progressive disease. CLL patients with autoimmune haemolytic anaemia / thrombocytopenia should have treatment for their immune cytopena and may not require antileukaemic treatment. High lymphocyte count alone without rapid lymphocyte doubling time may not warrant treatment as lymphocytosis rarely causes hyperviscosity. Treatment of CLL patients with cholelithiasis in their early stage (Binet A) had been shown to have no survival advantage when compared to deferring treatment until progression14.

Chemotherapy: If treatment is indicated, chlorambucil has been the standard first-line therapy since 1960s until the appearance of purine analogues in 1990s. Fludarabine as a single agent has been shown by large randomised studies and a meta-analysis of randomised studies to be able to induce higher complete remission rates when compared with chlorambucil. Response rates are further improved by fludarabine-containing combination regimens especially by the fludarabine plus cyclophosphamide combination15. It is recommended that this therapy is the treatment of choice for CLL patients who have no contraindications to fludarabine. However in elderly patients, especially those with comorbidities, the toxicity and side effects of such therapy might counterbalance the potential efficacy. First-line chlorambucil may be more suitable for these patients. Fludarabine is now available in Hong Kong in both the intravenous and the oral form. Ongoing studies are testing the clinical benefit of early treatment with fludarabine-based chemotherapy in a specific population of CLL patients with stage A disease and poor risk biological features.

Immunotherapy /chemo-immunotherapy: Promising effect is seen when rituximab (R), an anti-CD20 monoclonal antibody, is used in combination with fludarabine-base therapy, especially the fludarabine and cyclophosphamide (FCR), which has been demonstrated to achieve complete remission rates as high as 70%16. Alemtuzumab (anti-CD52), another un conjugated, humanised, monoclonal antibody given intravenously or subcutaneously has been proven to be an effective salvage therapy for CLL patients refractory to chemotherapy agents and fludarabine. The overall response rate is about 33%17 and most studies reported a median response duration of about 12 months.

Stem cell transplantation: For selected poor risk CLL patients, or patients who relapse after the above treatment, stem cell transplantation may be an option. Autologous stem cell transplantation may prolong remission duration but is not curative and carries a 5-10% transplant related mortality. Allogeneic stem cell transplantation is the only potentially curative treatment. Unfortunately it has a procedure-related mortality as high as up to 50%18. It has been observed that this high mortality rate may be reduced if patients identified as having high risk of progressive disease are transplanted at an earlier course of the disease when they are less heavily treated before the transplant. Its other setback is that most CLL patients are above 55 years of age and are not suitable candidates for allogeneic stem cell transplantation with conventional conditioning regimen. Recent advances in non-myeloablative stem cell transplant may be a more tolerable alternative.

References