Chronic lymphocytic leukaemia—new drugs and management

CME lecture

Getting the diagnosis right

It has recently become apparent that in many previous studies of chronic lymphocytic leukaemia (CLL) the data are contaminated by the inclusion of patients with other low grade lymphoproliferative diseases. Two, in particular, have been sources of error.

*Splenic lymphoma with villous lymphocytes* (SLVL) [1] is a relatively benign condition in which splenomegaly is universal and lymphadenopathy rare. A leukaemia is present, the leukaemic cells characteristically bearing cytoplasmic villi at one pole. In the REAL classification [2] the disease would be classified as splenic marginal zone lymphoma. Thrombocytopenia, when it occurs, is likely to be one of the features of hypersplenism. Thus splenomegaly and thrombocytopenia are much less sinister than they would be in CLL.

The presence of the T cell marker CD5 on the tumour B cells is the hallmark of CLL. *Mantle cell lymphoma* (MCL) [3] also has CD5 positive B cells, but it is much more malignant than CLL. Widespread lymphadenopathy is usually present, and the white cell count increases at a rapid rate. The leukaemic cells are much more pleomorphic than CLL cells, and the surface immunoglobulin is dense rather than sparse. Most MCL cells also have the t(11;14) chromosomal translocation with consequent up-regulation of the proto-oncogene *BCL-1*. I do not believe that this ever occurs in CLL. MCL is probably incurable and is usually rapidly fatal. Since it is much more likely to be referred to tertiary centres than CLL, it is frequently included in large series in the literature, particularly those from the USA.

Every effort should be made to get the diagnosis of CLL right. An experienced morphologist should look at the blood film. Cell markers and karyotype are helpful (Table 1) [4].

Picking losers in CLL

Two staging systems are currently in use (Tables 2 and 3) [5,6]. I prefer to use a combination of the two. Other factors which help to predict poor prognosis are a lymphocyte doubling time of less than 1 year, diffuse lymphocytic infiltration in the bone marrow trephine, and trisomy 12 in the karyotype [7]. We have recently shown that atypical morphology (more than 15% prolymphocytes, more than 10% cleaved or lympho-plasmacytoid cells) is one of the strongest adverse characteristics [8].

Avoiding treatment

On the principle of ‘first do no harm’ every effort should be made to avoid treating patients with CLL. The Medical Research Council’s first and second CLL trials both showed that there was no advantage in treating stage A patients with chlorambucil at presentation rather than waiting until they become symptomatic or progressive [9]. A meta-analysis of all such trials worldwide shows that there is a small but significant survival advantage in not treating stage A patients. Indeed, stage A patients without additional adverse features follow the same survival curve as age and sex matched normal individuals.

Whither anthracyclines?

Most authorities recommend treating stage B and C patients, although an argument could be made that not all stage B patients need treatment, and that it is necessary to ensure that anaemia and thrombocytopenia are due to marrow failure and not to an incidental cause. The first line drug is chlorambucil. It is

| Marker | CLL | SLVL | MCL |
|--------|-----|------|-----|
| Surface Ig | sparse | dense | dense |
| CD5 | pos | neg | pos |
| CD19 | pos | pos | pos |
| CD20 | pos | pos | pos |
| CD22 | neg | pos | neg |
| CD23 | pos | neg | neg |
| CD37 | pos | pos | pos |
| FMC7 | neg | pos | pos |
| Chromosomes | trisomy 12 del 13q14 | various | t(11;14) |

This article is based on a lecture given during a College CME day, ‘Haematology for general physicians’, on 7 June 1995 by Terry J Hamblin DM FRCP FRCPath, Professor of Immunohaematology, University of Southampton.
cheap and has few side effects. In trials it tends to be given in doses of 10 mg/m²/day for 6 days every 28 days until maximum response is achieved. In real life it is often used in smaller doses (such as 5–10 mg/day) for two weeks out of four until the disease reverts to stage A.

Do stage C patients benefit from the addition of an anthracycline? Although some trials have indicated no benefit for more intensive regimens, a French trial showed a survival advantage for patients receiving CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) [10]. What was remarkable about this trial was the low dose of doxorubicin (25 mg/m²/day) and the small number of patients required to achieve statistical significance. The current MRC CLL3 trial is investigating the value of anthracyclines in CLL. It compares chlorambucil and epirubicin with chlorambucil alone in stage B and stage C CLL. It is important that this trial should continue to recruit in order to settle this question.

Nucleoside derivatives

Three new and related agents have recently been introduced for the treatment of low grade lymphomas, including CLL. They all have a similar chemical structure, a similar spectrum of activity and similar side effects.

Fludarabine has been studied extensively at the MD Anderson Cancer Center in Houston. In previously treated patients with CLL there was a 57% response rate, with 13% complete responses and a further 16% in whom the only detectable residual disease was the presence of lymphoid nodules in the bone marrow trephine (nodular partial response). In previously untreated patients 74% achieved a complete or nodular partial response [11], and in some complete remissions the disease is undetectable even by PCR amplification [12]. Remissions in previously treated patients last on average for 2 years, and in untreated patients for an average of 3 years [13]. Fludarabine also has useful activity in follicular lymphoma and Waldenström’s macroglobulinaemia.

Fludarabine is given in a dose of 25 mg/m²/day for 5 days every 28 days. Myelotoxicity is the dose limiting toxicity, but there is also a progressive fall in CD4 positive lymphocyte numbers to levels seen in patients with AIDS (from a median of 1.015 x 10⁹/l to 0.169 x 10⁹/l after 3 months’ treatment. Despite this, most patients do not suffer from opportunistic infections [14].

Cladribine (chlorodeoxyadenosine) was introduced for the treatment of hairy cell leukaemia (HCL) but is a useful agent in CLL. A remission rate of 50% has been reported in previously treated patients [15]. The normal dose is 4 mg/m²/day for 7 days every 28 days. Side effects are very similar to those of fludarabine although thrombocytopenia is perhaps more severe.

Pentostatin (deoxycoformycin) is also primarily prescribed for HCL but may be used in CLL. Response rates of about 25% have been reported in previously treated cases [16,17]. The dose is 4 mg/m² weekly. There is evidence that some patients will respond to one nucleoside derivative yet be resistant to others [18].

The place of nucleoside derivatives in the treatment of CLL has yet to be determined. They are un-

---

### Table 2. Binet staging system for CLL

| Stage | Fewer than three involved sites* |
|-------|----------------------------------|
| Stage A |                                 |
| Stage B | Three or more involved sites*    |
| Stage C | Hb < 100 g/l or platelets < 10 x 10⁹/l |

*Sites of involvement are cervical, axillary and inguinal lymph nodes, spleen and liver.

### Table 3. Rai staging system for CLL

| Stage | Lymphocytosis only |
|-------|--------------------|
| Stage I | Lymphocytosis plus lymphadenopathy |
| Stage II | Lymphocytosis plus splenomegaly |
| Stage III | Lymphocytosis plus anaemia Hb < 110 g/l |
| Stage IV | Lymphocytosis plus thrombocytopenia platelets < 100 x 10⁹/l |

---
doubtedly good second line agents, and better than the anthracyclines at rescuing patients whose disease is resistant to chlorambucil. However, the cost to the NHS of 1 week’s treatment with fludarabine is £650. There is at present no evidence that it should supplant chlorambucil as first line treatment.

**Biological agents**

Interferon α has no effect in advanced disease although it may lower the white cell count in stage A disease. Monoclonal antibodies directed against CD5, CD19, CD20, CD37 and CD52 have all been used experimentally as murine, chimaeric or humanised derivatives and as immunotoxins. Promises have yet to be kept.

**Bone marrow transplantation**

Two similar studies have been published, Rabinow et al [19] treated 8 patients with T-cell depleted matched sibling allografts and 12 with monoclonal antibody purged marrow autografts. Achievement of remission was required before transplantation. Their median age was 40, although five were over 50. There were two toxic deaths. Ninety per cent achieved a complete immunological and molecular remission. Actuarial survival at 2 years was 60%. Khouri et al [20] treated 22 patients, whose median age was 47.5, with 11 over 50. Of 11 who had an anti-CD19 purged autologous marrow transplant, six achieved a complete and five a partial response. Of the other 11 who underwent allo- genetic transplant seven achieved a complete response. At 2 years the actuarial survival was 90% for the allogeneic group; it was 40% for the autologous group, three of whom developed Richter’s syndrome (a high grade lymphoma which is sometimes clonally related to the CLL).

The next MRC trial may well examine the role of bone marrow transplantation for younger patients with CLL.

**Conclusions**

Future studies on CLL should guard against contaminating data with cases of SLVL and MCL. Treatment of CLL in stage A patients should be delayed until the disease progresses. For more advanced cases chlorambucil is still the drug of choice. The place of anthracyclines remains to be established in a controlled trial. The nucleoside derivatives are useful second line agents; their place as first line agents needs to be determined by a controlled trial. Bone marrow transplantation may have a place in the treatment of the younger patient.

**References**

1. Matutes E, Morilla R, Owusu-Ankomah K, Houlihan A, Catovsky D. The immunophenotype of splenic lymphoma with villous lymphocytes and its relevance to the differential diagnosis with other B-cell disorders. *Blood* 1994;83:1558-62.
2. Harris NL, Jaffe ES, Stein H, Banks PM, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994; 84:1361-92.
3. Banks P, Chan J, Cleary M, Delsol G, et al. Mantle cell lymphoma: a proposal for unification of morphologic, immunologic and molecular data. *Am J Surg Pathol* 1992;16:637-40.
4. Bennett J, Catovsky D, Daniel M-T, Flandrin G, et al. Proposals for the classification of chronic (mature) B and T lymphoid leukemias. *J Clin Pathol* 1989;42:567-84.
5. Binet JL, Auquier A, Dighiero G, Chastang C, et al. A new prognostic classification of chronic lymphocytic leukaemia derived from a multivariate survival analysis. *Cancer* 1981;48:198-206.
6. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, et al. Clinical staging of chronic lymphocytic leukaemia. *Blood* 1975; 46:219-34.
7. Catovsky D. Chronic lymphoproliferative disorders. *Curr Opin Oncol* 1995;7:3-11.
8. Osier DG, Copplestone JA, Chapman R, et al. Atypical lymphocyte morphogenesis and abnormal karyotype predict disease progression in stage A and A0 chronic lymphocytic leukaemia. *Blood* 1994;84(suppl 1):452a.
9. Catovsky D, Richards S, Fooks J, Hamblin TJ. CLL trials in the United Kingdom: the Medical Research Council CLL trials 1, 2 and 3. *Leuk Lymphoma* 1991;5(suppl):105-12.
10. French Cooperative Group on Chronic Lymphocytic Leukaemia. Is the CHOP regime a good treatment for advanced CLL? Results from two randomized clinical trials. *Leuk Lymphoma* 1994;13:449-56.
11. Keating MJ, O’Brien S, Plunkett W, Robertson LE, et al. Fludarabine phosphate: a new active agent in hematologic malignancies. *Semin Hematol* 1994;31:28-39.
12. Richardson DS, Johnson SA, Hopkins JA, Howe D, Phillips MJ. Absence of minimal residual disease detectable by FACS, Southern blot or PCR in patients with chronic lymphocytic leukaemia treated with fludarabine. *Acta Oncol* 1994;33:627-30.
13. Keating MJ, O’Brien S, Kantarjian H, Plunkett W, et al. Long-term follow-up of patients with chronic lymphocytic leukemia treated with fludarabine as a single agent. *Blood* 1993; 81:2878-84.
14. O’Brien S, Kantarjian H, Beran M, Smith T, et al. Results of fludarabine and prednisone therapy in 264 patients with chronic lymphocytic leukemia with multivariate analysis-derived prognostic model for response to treatment. *Blood* 1993;82:1693-700.
15. Montserrat E, Rozman C. Chronic lymphocytic leukaemia treatment. *Blood Rev* 1993;7:164-75.
16. Dillman RO, Mick R, McIntyre OR. Pentostatin in chronic lymphocytic leukaemia: a phase I/II trial of cancer and leukaemia group B. *J Clin Oncol* 1989;7:433-8.
17. Ho AD, Thaler J, Stryckmans P, Coiffier B, et al. Pentostatin in refractory chronic lymphocytic leukaemia: a phase II trial of the European Organisation for Research and Treatment of Cancer. *J Natl Cancer Inst* 1990;82:1416-20.
18. Julio-Suarez G, Elmhorn-Rosenborg A. Lilemark J. Response to 2-chlorodeoxyadenosine in patients with B-cell chronic lymphocytic leukaemia resistant to fludarabine. *N Engl J Med* 1992; 327:1056-61.
19. Rabinow SN, Soiffer RJ, Gribben JG, Daley H, et al. Autologous and allogeneic bone marrow transplantation for poor prognosis patients with B-cell chronic lymphocytic leukaemia. *Blood* 1993;82:1366-76.
20. Khouri IF, Keating MJ, Vriesendorp HM, Reading CL, et al. Autologous and allogeneic bone marrow transplantation for chronic lymphocytic leukaemia: preliminary results. *J Clin Oncol* 1994;12:748-58.

Address for correspondence: Professor Terry J Hamblin, Department of Haematology, Royal Bournemouth Hospital, Castle Lane East, Bournemouth BH7 7DW.