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Review

Key Issues in the Treatment of Chronic Lymphocytic Leukaemia (CLL)

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The outcome of the treatment of chronic lymphocytic leukaemia (CLL) has improved little over the past 30 years. The recent introduction of purine analogues, particularly fludarabine, may change this situation. These agents are highly effective and generally well tolerated. They raise the possibility of improved disease-free survival and allow appropriate patients to be considered for bone marrow transplantation (BMT). Randomised clinical trials are needed to establish the roles of purine analogues and other novel agents in improving the survival of CLL patients. These trials should use consistent diagnostic and assessment criteria to allow for the clinical heterogeneity of CLL.

Key words: chronic lymphocytic leukaemia (CLL), purine analogues, prognostic factors
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INTRODUCTION

CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) is often described as an "indolent" disease, but this is not the case in at least 50% of patients [1]. Examination of survival curves shows that many patients die early, and the absence of a plateau shows that CLL is usually not cured (Figure 1). It is also important to consider that many patients die of causes not directly related to CLL. The overall median survival is approximately 6 years, and this has changed little over the past 30 years [1]. Recent advances in the diagnosis and treatment of CLL may improve this situation [2]. This article examines key issues that need to be addressed to optimise the treatment of this disease.

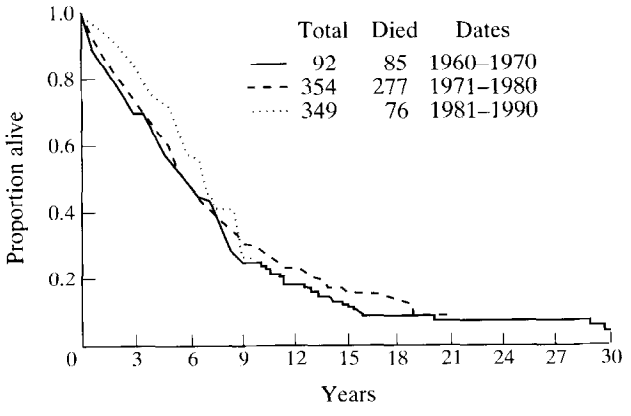

Figure 1. Survival of patients with untreated CLL by decade (MD Anderson Cancer Center). Reproduced with permission from Keating M. Chemotherapy of chronic lymphocytic leukaemia. In Cheson BD, ed. *Chronic Lymphocytic Leukemia. Scientific Advances and Clinical Developments.* New York, Marcel Dekker, 1993, 297–336.

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DIAGNOSIS OF CLL

The diagnosis of CLL depends on the detection of lymphocytosis in the blood and bone marrow. Threshold peripheral blood lymphocyte counts of 5×10^9/l and 10×10^9/l have been recommended by the National Cancer Institute Working Group on CLL (NCIWG) [3] and the International Workshop on CLL (IWCLL) [4], respectively. Differential counts of bone marrow aspirates must reveal that over 30% of all nucleated cells are mature-appearing B-lymphocytes. Examination of peripheral blood films is useful to confirm that the malignant cells are lymphocytes, which usually have distinct nuclear chromatin clumping.

Immunophenotyping is an essential tool for distinguishing CLL from other B-cell or T-cell disorders [5]. Recent results indicate that no single immunological marker is completely specific for CLL, but examination of several markers reveals a profile that objectively distinguishes CLL from other disorders in the majority of cases [6].

PROGNOSTIC FACTORS

The course of CLL varies widely between patients, therefore, prognostic factors must be evaluated to predict the course of the

disease and select the most appropriate treatments. The principle prognostic factors identified to date are summarised below.

Age

Older patients have a poorer prognosis than younger patients [7–10]. A recent survey has indicated that when non-CLL causes of death are excluded, younger patients (< 50 years) have no better survival than older patients [11]. This result suggests that prognostic indicators are no different in the two age groups, and that the shorter survival in older patients is a consequence of unrelated diseases. The median survival in patients aged < 50 years, who account for 5–7% of patients, is at least 20 years shorter than comparable controls [8, 11]. These observations justify the evaluation of more intense treatments in younger patients with advanced disease and other poor prognostic factors.

Sex

Women with CLL have a better prognosis than men, even after correction for other factors including age and stage [10, 12]. The reason for this is not fully understood.

Clinical stage

Staging, using either the Rai or Binet systems, is the most important prognostic factor for survival in CLL (Figure 2) [10, 13, 14]. The patients with the worst prognosis are those in Binet stage C, which is equivalent to Rai stages III and IV. The IWCLL has proposed a classification that combines the Rai and Binet systems and identifies distinct subgroups within the stages [3]. This system has not been widely adopted, although the best prognosis within stage A is the subgroup A (0).

Lymphocyte count and doubling time

The NCIWG and the IWCLL have defined lymphocytosis at thresholds of 5×10^9/l and 10×10^9/l, respectively [2, 3], although it has been suggested that a diagnosis of CLL could be made with lower counts [15]. Immunophenotyping to confirm the diagnosis is essential, particularly in cases with low lymphocyte counts. A high lymphocyte count correlates with advanced clinical stage and a poor prognosis [6, 12].

In patients with Binet stages A and B, a lymphocyte doubling time of less than 12 months correlates with more rapid progression and shorter survival [16, 17]. The NCIWG regards a doubling time of less than 6 months as an indication for treatment [2]. Data from the Medical Research Council (MRC) CLL3 trial appear to confirm the strong prognostic value of a lymphocyte doubling time < 12 months compared with > 12 months (D. Catovsky, unpublished observations).

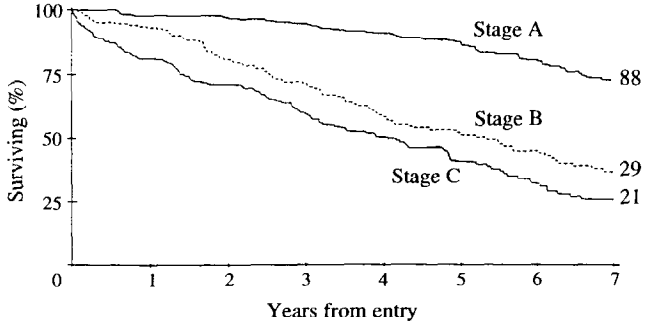

Figure 2. Survival of patients with CLL by Binet/International stage entered in MRC CLL 1 trial [10]. Only CLL-related deaths were considered. Numbers shown indicate the number of patients alive 7 years after entry into the study. Reproduced with permission from Catovsky D, Fooks J, Richards R. Prognostic factors in chronic lymphocytic leukaemia: the importance of age, sex and response to treatment in survival. A report from the MRC CLL 1 trial. *Br J Haematol* 1989, 72, 141–149.

Bone marrow pattern

A trephine biopsy should be a standard investigation in CLL. A diffuse or packed pattern of bone marrow infiltration confers a worse prognosis than a non-diffuse (nodular, interstitial or mixed) pattern. As a diffuse pattern is correlated with a more advanced clinical stage, the independent significance of the bone marrow pattern has not been shown in all studies [18–20]. This information is more important in patients with intermediate prognosis, such as Binet stage B. In this group, a packed bone marrow identifies the group with worse prognosis [18].

Chromosomal abnormalities

Chromosomal abnormalities, most commonly trisomy 12 and 13q deletions, have been detected in approximately 50% of patients with CLL in whom suitable metaphases could be obtained. Cytogenetic analysis is not a routine investigation in CLL and it is not easy to obtain suitable metaphases. In recent years, therefore, fluorescence *in situ* hybridisation (FISH) techniques have been used to detect trisomy 12 in interphase nuclei [21]. A recent investigation, in which FISH and immunophenotyping were performed simultaneously in single interphase cells, showed that trisomy 12 is a secondary event during the leukaemic transformation of CLL and develops in an already established neoplastic B-cell population [22]. Trisomy 12 appears to correlate with worse prognosis, either because it is associated with a typical morphology, particularly CLL-PL [21] and/or because it confers a growth advantage on the malignant cells [22]. A high number of chromosomal abnormalities also predicts a poorer outcome [23–25].

Oncogenes

Activation of oncogenes has, so far, been identified in only a small proportion of patients with CLL. Expression of *bcl-2*, found in 5–10% of patients [26], produced an oncoprotein that inhibits apoptosis in lymphocytes [27] and may confer resistance to cytotoxic agents [28]. The alteration of the *bcl-2* oncogene in CLL is distinct from that seen in follicular lymphoma [29].

Response to treatment

A good response to treatment is associated with longer survival independently of age, sex or disease stage [10]. As a good response is associated with other favourable factors, such as early clinical stage and no previous treatment, the value of this parameter could only be assessed in randomised trials.

DEFINING RESPONSE TO TREATMENT

The NCIWG [3] and the IWCLL [4] have published guidelines to facilitate comparisons between clinical trials in CLL in different centres (Tables 1 and 2). The criteria used in MRC trials 1, 2 and 3 are similar to the NCI criteria.

The NCI criteria for a complete response (CR) allow the persistence of nodules in the bone marrow. This response has been called a "nodular CR" (nCR) to distinguish it from a CR with a normal bone marrow. In one series, patients with a nCR after fludarabine had a shorter time to disease progression than patients with a CR, but their survival was not significantly different [30]. As persistent nodular infiltration predicts earlier

Table 1. *NCI guidelines for CLL* [11]*

Diagnosis	
Lymphocytes	$> 5 \times 10^9$/l
Atypical cells (e.g. prolymphocytes)	< 55%
Duration of lymphocytosis	≥ 2 months
Bone marrow lymphocytosis	≥ 30%
Staging	Modified Rai, correlate with Binet
Eligibility for trials	"Active disease" (loss of ≥ 10% of body weight in last 6 months; extreme fatigue; fever > 100.5°F for ≥ 2 weeks unrelated to infection; night sweats; anaemia, thrombocytopenia; autoimmune anaemia and/or thrombocytopenia not responding to steroids) Massive splenomegaly or lymphadenopathy Progressive lymphocytosis with an increase of > 50% in 2 months or doubling time < 6 months
Criteria for complete response	
Physical examination	Normal
Symptoms	None
Cell count	Lymphocytes ≤ 4×10^9/l, neutrophils ≥ 1.5×10^9/l, platelets > 100×10^9/l
Haemoglobin	> 11g/dl (untransfused)
Bone marrow lymphocytes in aspirates	< 30%
Duration	≥ 2 months
Criteria for partial response (used in MRC CLL trials)	
Physical examination	≥ 50% decrease in nodes and/or liver/spleen
Plus one of:	Neutrophils ≥ 1.5×10^9/l, platelets > 100×10^9/l, haemoglobin > 11 g/dl or > 50% improvement
Duration	≥ 2 months
Criteria for progressive disease	
Physical examination (nodes, liver, spleen)	≥ 50% increase or new
Circulating lymphocytes	≥ 50% increase
Other	Richter's syndrome
Criteria for stable disease	All others

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relapse, nCR might better be designated "nodular partial response" (nPR).

Two-colour flow cytometry, immunophenotypic analysis, FISH and the polymerase chain reaction may help to assess residual disease in patients with a clinical CR [31–33]. In a recent study on 22 patients in clinical CR, residual disease, detected by light chain restriction dual CD5/CD9 staining and Ig gene rearrangement, was associated with a shorter disease-free interval than in patients with negative findings on these tests [34].

CURRENT TREATMENTS FOR CLL

Indications for treatment

Patients with CLL can be stratified into three groups:

(i) high risk (median survival 1.5–5 years): Binet stage C; Rai III or IV
(ii) intermediate risk (median survival 5–7 years): Binet stage B; Rai I or II
(ii) low risk (median survival > 10 years): Binet stage A; Rai 0.

High risk patients suffer frequent complications, so should be treated as soon as they have been fully evaluated. At diagnosis, most patients fall into the intermediate or low risk groups. These individuals can follow an indolent course, in which CLL progresses slowly and the patient remains asymptomatic for a long period. Patients with indolent Rai 0 or Binet A CLL (smouldering CLL) can survive as long as age- and sex-matched controls. The active disease can be manifested by increasing lymphocytosis and other signs and symptoms (e.g. lymphadenopathy, anaemia, thrombocytopenia, infections), in a variable proportion of patients. Randomised trials have shown that administration of chlorambucil to stage A patients delays progression, but does not improve survival compared with delaying treatment until progression occurs, and might even be harmful [35, 36]. Low or intermediate risk patients may be followed without treatment until signs of disease activity, or adverse prognostic factors, are observed. In practice, stage B patient are treated, although a randomised trial of early or delayed treatment in this group could be considered. Even patients with indolent disease must be assessed regularly because some of them will progress [37]. It is in this group that determination of the lymphocyte doubling time may be important.

Table 2. IWCLL guidelines for CLL [12]*

Diagnosis	
Lymphocytes	$\geq 10 \times 10^9$/l + B phenotype or bone marrow involved; $< 10 \times 10^9$/l + B phenotype and bone marrow involved
Atypical cells (e.g. prolymphocytes)	Not stated
Duration of lymphocytosis	Not stated
Bone marrow lymphocytosis	> 30%
Staging	IWCLL
Eligibility for trials	Stage A: lymphocytes $> 50 \times 10^9$/l, and/or doubling time < 12 months and/or diffuse marrow Stage B, C: all patients
Criteria for complete response	
Physical examination	Normal
Symptoms	None
Lymphocytes	$< 4 \times 10^9$/l
Neutrophils	$> 1.5 \times 10^9$/l
Platelets	$> 100 \times 10^9$/l
Haemoglobin	Not stated
Bone marrow lymphocytes in aspirates	"Normal", allowing nodules or focal infiltrates
Duration	Not stated
Criteria for partial response	Downshift in stage (cell counts not stated)
Duration	Not stated
Criteria for progressive disease	Upshift in stage
Criteria for stable disease	No change in stage

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First-line treatment

Chlorambucil is the standard first-line treatment for CLL. It reduces the lymphocyte count in approximately two-thirds of patients and, in a smaller proportion, reduces spleen size and improves platelet counts and haemoglobin [38–41]. Chlorambucil is given orally and it is generally well tolerated. Many centres combine chlorambucil with prednisone, although there is no evidence that addition of this drug, or prednisolone [36], confers any survival benefit. Chlorambucil plus prednisone induces CRs in approximately 25% of patients and PRs in approximately 50% [42–48]. Chlorambucil has been given daily in the past; lately, intermittent dosing has been used more commonly. This modality has similar efficacy and is less toxic [41]. The schedule currently used in the MRC CLL3 trial is chlorambucil, 10 mg/m^2 daily for 6 days, repeated monthly. High dose continuous chlorambucil has been reported to give greater response rates and longer survival than intermittent chlorambucil plus prednisone in stage A and B patients [49]. This regimen could be tested further, but in a properly randomised trial.

Cyclophosphamide can be used alone in patients who cannot tolerate chlorambucil, but there is no good evidence for its single agent activity. It is used mostly in combination regimens (see below).

Prednisone given alone has only modest effects in the primary treatment of CLL [38, 50], but it is valuable in the treatment of autoimmune anaemia or thrombocytopenia [15]. In the early treatment of stage C (or stage III–IV) disease, corticosteroids alone may improve bone marrow function and facilitate subsequent treatment with cytotoxic agents [10].

Treatment of relapsed/refractory CLL

In patients who are refractory to chlorambucil, or who relapse shortly after an initial response, repeated administration of chlorambucil is often ineffective and the median survival is approximately 15 months [51]. Combination regimens are frequently used in these patients, the most widely used being COP (cyclophosphamide, vincristine and prednisone), CAP (cyclophosphamide, doxorubicin and prednisone) and CHOP (COP + doxorubicin), POACH (cyclophosphamide, doxorubicin, vincristine, cytosine arabinoside and prednisone) and M2 (vincristine, cyclophosphamide, BCNU, melphalan and prednisone) have also been tried. With all these regimens, the response rates are typically 25–35%, with very few CRs, and toxicity is common [44, 47, 51–54].

Randomised trials, mainly in refractory or advanced disease, have failed to show a survival advantage of COP or CHOP over chlorambucil with or without prednisone [36, 45, 46, 55] or of CHOP over chlorambucil with prednisolone [56], despite higher response rates in some studies. A report that stage C patients treated with CHOP survive longer than those treated with COP [57, 58] has not been confirmed by other investigators, and a large overview meta-analysis is currently in progress. In stage C patients, a trial of CHOP versus CHOP with methotrexate failed to show a response or survival difference [56].

It can be argued that trials of CHOP versus chlorambucil test not only the role of the anthracycline, but also the contribution of other drugs in the combination (e.g. cyclophosphamide). For that reason, the MRC CLL3 trial is currently comparing chlorambucil with chlorambucil at the same dose plus epirub-

icin. So far, 300 patients have been randomised, but the results will not be known for some time.

Splenectomy

Splenectomy should be considered if hypersplenism is believed to be the cause of anaemia or thrombocytopenia which has not responded to chemotherapy and corticosteroids. It can induce a prolonged remission in patients whose disease is predominantly localised to the spleen, or in whom a good response to treatment is obtained in all organs except the spleen [15, 59]. If the disease is localised to the spleen, other diagnoses (e.g. splenic lymphoma with villous lymphocytes (SLVL) or mantle-cell lymphoma) should be considered.

Radiation therapy

Radiation therapy is used mainly to reduce enlarged lymph nodes that are painful, unsightly, or compressing vital organs. Low dose total body irradiation (TBI) has been used as a primary therapy for CLL in a few studies. It is no more effective than chemotherapy, and it is frequently associated with severe myelosuppression [60, 61]. In MRC CLL trials 1 and 2, splenic irradiation did not, overall, prove to be superior (or inferior) to cytotoxic drugs [36].

Treatment of infections

Infections are responsible for over half the disease-related deaths in CLL [10]. Most of the infections are bacterial, and pneumonias are their most common manifestation. Mycoses and viral infections also occur. The main cause of infection is hypogammaglobulinaemia. A further cause of infections is alteration of cell-mediated immunity by purine analogues, which, in addition to causing neutropenia by bone marrow toxicity, selectively reduce CD4+ lymphocytes. As a result, atypical infections not seen previously in CLL, such as *Pneumocystis carinii* pneumonia, Listerosis and aspergillosis, have been reported in patients receiving these drugs, most often in non-responders [62–64].

Immunisation is usually ineffective in CLL [65], so antibiotic prophylaxis forms the principle treatment for infections. For most patients, amoxicillin or ampicillin/clavulanic acid, which are active against most upper respiratory tract pathogens, are appropriate. Patients receiving purine analogues should receive prophylaxis for opportunistic infections. For example, the MCR investigators prescribe co-trimoxazole and add oral acyclovir if lymphopenia is marked. Intravenous immunoglobulins have been successful in reducing the frequency of infections in CLL [66].

PURINE ANALOGUES

Mechanisms of action

The purine analogues that have been investigated in CLL are 2′-deoxycoformycin (2-DCF), 2-chlorodeoxyadenosine (2-CDA) and fludarabine. The principle effect of 2-DCF is inhibition of adenosine deaminase, leading to accumulation of deoxyadenosine triphosphate, which inhibits ribonucleotide reductase and inhibits DNA replication and repair [67]. 2-CDA inhibits the synthesis of DNA by inhibiting DNA polymerases and ribonucleotide reductase [68]. Fludarabine inhibits DNA polymerase α, β, γ and ϵ, and DNA ligase, and, following incorporation into DNA, is a highly effective chain terminator [69, 70]. This compound is unique among purine analogues in that it can also inhibit synthesis of RNA [71, 72]. The activity of purine analogues against quiescent cells, which form the majority of malignant cells in CLL, is a result of disruption of nucleotide pools, which inhibits DNA repair and results in apoptosis [73–75].

Clinical trials with fludarabine

Most clinical trials with fludarabine have been performed in relapsed or refractory CLL [76–84]. The recommended dose is 25 mg/m^2/day for 5 days by 30 min intravenous (i.v.) infusion or i.v. push, repeated every 4 weeks. The overall response rates are 40–55%, as high as is achieved with combination regimens, and the CR rates are higher at approximately 13%. Alternative regimens, including once-weekly dosing [83], are less effective.

In previously untreated CLL, fludarabine induced CR in 33% of patients and a nPR in a further 40%, to give a CR rate of 73% according to NCI criteria [30, 84]. This is the highest response rate ever recorded with a single agent in CLL (although the nPR has been considered as "nodular CR" in the MD Anderson studies). In younger patients, the achievement of CR may facilitate further high dose therapy with autologous transplantation procedures.

Fludarabine was generally well tolerated in these trials. The main adverse events were myelosuppression, infections (including some opportunistic infections) and fever of unknown origin. The infections probably resulted partly from the immune dysfunction that occurs in CLL and partly from myelosuppression and depletion of CD4+ lymphocytes [62–64]. Reversible pulmonary toxicity has also been reported [85].

The addition of prednisone to fludarabine does not improve response rates, and may increase the risk of opportunistic infections [86, 87]. Combinations of fludarabine with other agents are under investigation, but they are likely to be too toxic unless one compromises by using a lower dose of fludarabine than in single-agent therapy.

A long-term follow-up of patients treated with fludarabine alone was published recently [30]. Younger age, a smaller number of prior treatments, and a CR or nPR were associated with longer survival. Median time to progression after a response was 33 months in previously untreated patients and 22 months in those previously treated.

In a recent trial at the Royal Marsden Hospital, fludarabine was evaluated in 52 previously treated patients (D. Catovsky, unpublished observations). Most of the patients were refractory to chlorambucil and 12 had CLL-PL. The reponse rates are summarised in Table 3. Patients who achieved a CR or a PR had significantly greater survival than those who did not respond or were not evaluable (Figure 3). The time to disease progression in responders was not significantly different between CLL and CLL-PL (Figure 4).

Preliminary results from a comparative trial of fludarabine against CAP [82] and comparisons with previous trials [30] suggest that fludarabine induces slightly longer responses than

Table 3. Response rates to fludarabine in the Royal Marsden Hospital series (D. Catovsky, unpublished observations)

Disease type	No. of cases	CR (%)	PR (%)	CR + PR (%)
CLL	34*	6 (18)	14 (41)	20 (59)
CLL-PL	12	–	9 (75)	9 (75)
Overall	46	6 (13)	23 (50)	29 (63)

*Excludes 6 patients who died within 2 months and were not evaluable.

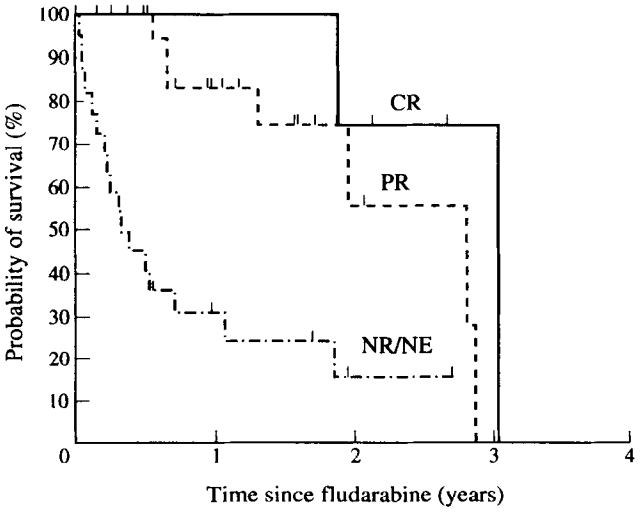

Figure 3. Survival of patients with CLL or CLL-PL (n = 46) (see Figure 4) by response to fludarabine in the Royal Marsden Hospital series (D. Catovsky, unpublished observations). CR, complete response; PR, partial response; NR/NE, no response/not evaluable. χ^2 = 19.34, df = 2, $P < 0.005$.

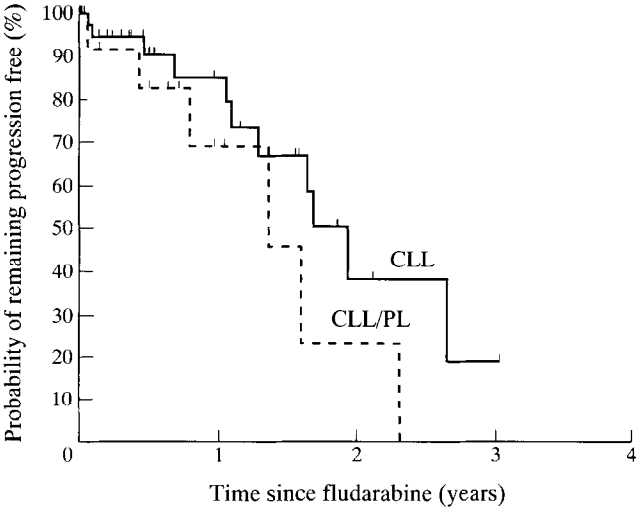

Figure 4. Probability of disease progression in patients in the Royal Marsden Hospital series (D. Catovsky, unpublished observations). CLL, chronic lymphocytic leukaemia; CLL-PL, CLL with increased prolymphocytes.

combination regimens, but the long-term survival is similar. Randomised trials are ongoing to clarify the effects of fludarabine on long-term survival, and determine whether it should be reserved for second-line treatment or used as first-line therapy.

Other purine analogues

Other purine analogues appear to be less promising than fludarabine in the treatment of CLL. 2-CDA induces response rates of 45–55% in previously treated patients, but CRs are less common than with fludarabine and are of shorter duration [88–90]. Myelosuppression and infection are the principal adverse events. 2-DCF induces response rates of 20–27%, with few CRs, and has been associated with opportunistic infections [91, 92].

IFN-α

IFN-α has been reported to reduce the lymphocyte counts in early CLL [93–97], but the responses are transient and no CRs have been observed. IFN-α is not effective in advanced disease [98]. The activity of IFN-α might be more appropriately tested in patients in remission, to see whether it can prolong the remission or improve survival.

HAEMATOPOIETIC GROWTH FACTORS

Recombinant granulocyte colony stimulating factor reduces neutropenia and infections in patients with non-Hodgkin's lymphoma receiving CHOP [99, 100], allowing the dose to be maintained or increased [101, 102]. Clinical trials are required to determine whether a similar effect could be achieved in patients with CLL treated with fludarabine.

BONE MARROW TRANSPLANTATION

Allogeneic and autologous BMT have recently been attempted in small groups of patients with poor prognosis CLL [103–107]. Various regimens, including TBI, CHOP and fludarabine, were used to induce a CR before transplantation. The results of three trials are summarised in Table 4 [103, 106, 107]. CRs, some of which were durable, were obtained in some patients. The main causes of death were relapse, graft-versus-host disease and toxicity of the conditioning regimen. These results suggest that it is possible to undertake BMT in patients with poor prognosis CLL. Favourable responses were obtained in some patients aged over 60 years. This indicates that clinical trials of BMT in CLL need not necessarily be restricted to younger patients.

MONOCLONAL ANTIBODIES

Monoclonal antibodies against B-cell antigens, either alone or combined with toxins or radioisotopes, have been attempted in a few patients [108]. The published results have been largely disappointing, probably because the antibodies cannot reach malignant cells in the bone marrow and lymph nodes, and

Table 4. Results of BMT in CLL in three recent trials

First author [Ref.]	No. of patients	Median age (years)	Type of transplant	% CR	% projected 2 year survival
Michallet [104]	17	40	Allogeneic	88	–
Rabinowe *et al.* [108]	20	40	Autologous (12) Syngeneic (8)	Almost 90*	60
Khouri *et al.* [107]	22	47.5	Allogeneic (11) Autologous (11)	Allogeneic (64) Autologous (55)	Allogeneic (90) Autologous (40)

*Documented by phenotype and Ig gene rearrangements.

because the malignant cells are capable of antigenic modulation. The humanised monoclonal CAMPATH 1H antibody, given subcutaneously, has shown promising results at our institution in patients with treatment-resistant CLL and B-prolymphocytic leukaemia (B-PLL) (D. Catovsky and M. Dyer, unpublished observations).

TREATMENT OF "CLL VARIANTS"

A number of B-cell disorders have been vaguely described as "CLL variants". The only disease closely related to CLL is CLL-PL, which consists of a CLL background with an increase in the prolymphocyte population. CLL-PL is a subtle transformation of CLL arising from the same clone, with a higher proliferation rate assessed by monoclonal antibody Ki-67 labelling and evidence of trisomy 12 in approximately half the cases [21].

Richter's syndrome is a transformation of CLL to a large-cell lymphoma [109]. Recent evidence indicates that half the cases of Richter's syndrome develop from the same CLL clone and the rest from a new B-cell clone [110]. The prognosis is poor, with median survival of 4–6 months. Combination regimens (e.g. CHOP) are the treatment of choice. The prognosis is strongly dependent on whether a remission can be obtained.

Other diseases, such as B-PLL, hairy cell leukaemia (HCL) and SLVL are distinct diseases [111]. CLL-PL and B-PLL seem to benefit from fludarabine [112–114], whereas HCL is treated with 2-CDA or 2-CDF. The treatment of choice for SLVL is splenectomy, although a minority of patients respond to fludarabine.

CONCLUSION

The introduction of new treatments, particularly the purine analogues, has stimulated renewed interest in CLL. The high efficacy and good overall tolerability of these agents raises the possibility of improved long-term survival, and the high CR rate allows BMT to be considered in younger patients. This represents a shift of emphasis in the treatment of CLL from palliative therapy to curative intent. Controlled clinical trials, with carefully identified subgroups of patients and rigorous diagnosis and assessment criteria, are required to define the place of new treatments and improve the outcome of this disease.

1. Keating M. Chemotherapy of chronic lymphocytic leukaemia. In Cheson BD, ed. *Chronic Lymphocytic Leukemia. Scientific Advances and Clinical Developments*. New York, Marcel Dekker, 1993, 297–336.
2. Catovsky D. Chronic lymphoproliferative disorders. *Curr Opin Oncol* 1995, **7**, in press.
3. Cheson BD, Bennett JM, Rai KR, *et al.* Guidelines for clinical protocols for chronic lymphocytic leukemia (CLL). Recommendations of the National Cancer Institute-Sponsored Working Group. *Am J Hematol* 1988, **29**, 152–163.
4. Binet J-L, Catovsky D, Dighiero G, *et al.* Chronic lymphocytic leukemia: recommendations for diagnosis, staging and response criteria. International Workshop on CLL. *Ann Intern Med* 1989, **110**, 236–238.
5. Bennett JM, Catovsky D, Daniel MT, *et al.* The French–American–British (FAB) Cooperative Group. Proposals for the classification of chronic (mature) B and T lymphoid leukaemias. *J Clin Pathol* 1989, **42**, 567–584.
6. Matutes E, Owusu-Ankomah K, Morilla R, *et al.* The immunological profile of B-cell disorders and proposal of a scoring system for the diagnosis of CLL. *Leukemia* 1994, **8**(10), 1640–1645.
7. French Cooperative Group on Chronic Lymphocytic Leukaemia. Natural history of stage A chronic lymphocytic leukaemia in untreated patients. *Br J Haematol* 1990, **76**, 45–57.
8. Lee JS, Dixon DO, Kantarjian HM, Keating MJ, Talpaz M. Prognosis of chronic lymphocytic leukemia: a multivariate regression analysis of 325 untreated patients. *Blood* 1987, **69**, 929–936.
9. Pines A, Ben-Bassat I, Modan M, Blumstein T, Ramot B. Survival and prognostic factors in chronic lymphocytic leukemia. *Eur J Haematol* 1987, **38**, 123–130.
10. Catovsky D, Fooks J, Richards R. Prognostic factors in chronic lymphocytic leukaemia: the importance of age, sex and response to treatment in survival. A report from the MRC CLL 1 trial. *Br J Haematol* 1989, **72**, 141–149.
11. Molica S, Brugiatelli M, Callea V, *et al.* Comparison of younger versus older B-cell chronic lymphocytic leukemia patients for clinical presentation and prognosis. A retrospective study of 53 cases. *Eur J Haematol* 1994, **52**, 216–221.
12. Pangalis GA, Reverter JC, Bousiotis VA, Montserrat E. Chronic lymphocytic leukemia in younger adults: preliminary results of a study based on 454 patients. *Leukemia Lymphoma* 1991, **5** (suppl. 1), 175.
13. Rai KR. A critical analysis of staging in CLL. In Gale RP, Rai KR, eds. *Chronic Lymphocytic Leukemia: Recent Progress and Future Direction*. New York, Alan R. Liss, 1987.
14. Binet JL, Auquier A, Dighiero G, *et al.* A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer* 1981, **48**, 198–206.
15. Rai KR. Clinical management of chronic lymphocytic leukemia. In Cheson BD, ed. *Chronic Lymphocytic Leukemia. Scientific Advances and Clinical Developments*. New York, Marcel Dekker, 1993, 241–251.
16. Montserrat E, Sanchez-Bisono J, Viñolas N, Rozman C. Lymphocyte doubling time in chronic lymphocytic leukaemia: analysis of its prognostic significance. *Br J Haematol* 1986, **62**, 567–575.
17. Molica S, Alberti A. Prognostic value of the lymphocyte doubling time in chronic lymphocytic leukemia. *Cancer* 1987, **60**, 2712–2716.
18. Rozman C, Montserrat E, Rodríguez-Fernández JM, *et al.* Bone marrow histologic pattern—the best single prognostic parameter in chronic lymphocytic leukemia: a multivariate survival analysis of 329 cases. *Blood* 1984, **64**, 642–648.
19. Han T, Barcos M, Emrich L, *et al.* Bone marrow infiltration patterns and their prognostic significance in chronic lymphocytic leukemia: correlations with clinical, immunologic, phenotypic, and cytogenetic data. *J Clin Oncol* 1984, **2**, 562–570.
20. Desablens B, Claisse JF, Piprot-Choffat C, Gontier MF. Prognostic value of bone marrow biopsy in chronic lymphoid leukemia. *Nouv Rev Fr Hematol* 1989, **31**, 179.
21. Que TH, Marco JG, Ellis J, *et al.* Trisomy 12 in chronic lymphocytic leukemia detected by fluorescence *in situ* hybridisation. Analysis by stage, immunophenotype, and morphology. *Blood* 1993, **81**, 143–150.
22. García-Marco J, Matutes E, Morilla R, *et al.* Trisomy 12 in B-cell chronic lymphocytic leukaemia: assessment of lineage restriction by simultaneous analysis of immunophenotype and genotype in interphase cells by fluorescence *in situ* hybridisation. *Br J Haematol* 1994, **87**, 44–50.
23. Han T, Henderson ES, Emrich LJ, Sandberg AA. Prognostic significance of karyotypic abnormalities in B-cell chronic lymphocytic leukemia: an update. *Semin Hematol* 1987, **24**, 257–263.
24. Bird ML, Ueshima Y, Rowley JD, Haren JM, Vardiman JW. Chromosome abnormalities in B-cell chronic lymphocytic leukemia and their clinical correlations. *Leukemia* 1989, **3**, 182–191.
25. Juliusson G, Oscier DG, Fitchett M, *et al.* Prognostic subgroups in B-cell chronic lymphocytic leukemia defined by specific chromosomal abnormalities. *N Engl J Med* 1990, **323**, 720–724.
26. Rechavi G, Katzir N, Brok-Simoni F, *et al.* A search for *bcl-1*, *bcl-2*, and *c-myc* oncogene rearrangements in chronic lymphocytic leukemia. *Leukemia* 1989, **3**, 57–60.
27. Hockenbery D, Nunez G, Milliman C, *et al.* Bcl-2 is an inner mitochondrial membrane protein that blocks programmed cell death. *Nature* 1990, **348**, 334–336.
28. Reed JC, Kitada S, Takayama S, Miyashita T. Regulation of chemoresistance by the *bcl-2* oncoprotein in non-Hodgkin's lymphoma and lymphocytic cell lines. *Ann Oncol* 1994, **5** (suppl. 1), S61–S65.
29. Dyer MJS, Zani VJ, Lu WZ, *et al.* Bcl2 translocations in leukemias of mature B cells. *Blood* 1994, **83**, 3682–3688.
30. Keating MJ, O'Brien S, Kantarjian H, *et al.* Long-term follow-

up of patients with chronic lymphocytic leukemia treated with fludarabine as a single agent. *Blood* 1993, **81**, 2878–2884.
31. Robertson LE, Huh YO, Butler JJ, *et al.* Response assessment in chronic lymphocytic leukemia after fludarabine plus prednisone. Clinical pathologic, immunophenotypic, and molecular analysis. *Blood* 1990, **80**, 29–36.
32. Soper L, Bernhardt B, Eisenberg A, *et al.* Clonal immunoglobulin gene rearrangements in chronic lymphocytic leukemia: a correlative study. *Am J Hematol* 1988, **27**, 257–264.
33. Escudier SM, Pereira-Leahy JM, Drach JW, *et al.* Fluorescent *in situ* hybridisation and cytogenetic studies of trisomy 12 in chronic lymphocytic leukemia. *Blood* 1993, **81**, 2702–2707.
34. Lenormand B, Bizer M, Fruchart C, *et al.* Residual disease in B-cell chronic lymphocytic leukemia patients and prognostic value. *Leukemia* 1994, **8**, 1019–1026.
35. The French Cooperative Group on Chronic Lymphocytic Leukemia. Effects of chlorambucil and therapeutic decision in initial forms of chronic lymphocytic leukemia (stage A): results of a randomized clinial trial of 612 patients. *Blood* 1990, **75**, 1414–1421.
36. Catovsky D, Richards S, Fooks J, Hamblin TJ. CLL trials in the United Kingdom—the Medical Research Council CLL trials 1, 2, and 3. *Leukemia Lymphoma* 1991, **5** (suppl. 1), 105–112.
37. Montserrat E, Viñolas N, Reverter J-C, Rozman C. Chronic lymphocytic leukemia in early stage: "smoldering" and "active" forms. In Cheson BD, ed. *Chronic Lymphocytic Leukemia. Scientific Advances and Clinical Developments*. New York, Marcel Dekker, 1993, 281–296.
38. Galton DAG, Wiltshaw E, Szur L, Dacie JV. The use of chlorambucil and steroids in the treatment of chronic lymphocytic leukaemia. *Br J Haematol* 1961, **7**, 73.
39. Ezdinli EZ, Stutzman L. Chlorambucil therapy for lymphomas and chronic lymphocytic leukemia. *JAMA* 1965, **30**, 359.
40. Kaung DT, Whittington RM, Spencer HH, Patno ME. Comparison of chlorambucil and streptonigrin (NSC-45383) in the treatment of chronic lymphocytic leukemia. *Cancer* 1969, **23**, 597.
41. Knopse WH, Loeb V Jr, Huguley CM Jr. Biweekly chlorambucil treatment of chronic lymphocytic leukemia. *Cancer* 1974, **33**, 555.
42. Han T, Ezdinli EZ, Shimaoka K, Desai DV. Chlorambucil vs combined chlorambucil–corticosteroid therapy in chronic lymphocytic leukemia. *Cancer* 1973, **31**, 502.
43. Keller JW, Knopse WH, Raney M, *et al.* Treatment of chronic lymphocytic leukemia using chlorambucil and prednisone with or without cycle-active consolidation chemotherapy. *Cancer* 1986, **58**, 1185–1192.
44. Raphael B, Andersen JW, Silber R, *et al.* Comparison of chlorambucil and prednisone versus cyclophosphamide, vincristine and prednisone as initial treatment for chronic lymphocytic leukemia: long-term follow-up of an Eastern Cooperative Oncology Group randomized clinical trial. *J Clin Oncol* 1991, **9**, 770–776.
45. Hansen MM, Andersen E, Birgens H, *et al.* CHOP versus chlorambucil + prednisolone in chronic lymphocytic leukemia. *Leukemia Lymphoma* 1991, **5**, 97–100.
46. Kimby E, Mellstedt H. Chlorambucil/prednisone versus CHOP in symptomatic chronic leukemias of the B-cell type. A randomized trial. *Leukemia Lymphoma* 1991, **5** (suppl. 1), 93–96.
47. Montserrat E, Alcalá A, Parody R, *et al.* Treatment of chronic lymphocytic leukemia in advanced stage: a randomized trial comparing chlorambucil plus prednisone versus cyclophosphamide, vincristine and prednisone. *Cancer* 1985, **56**, 2369–2375.
48. Montserrat E, Alcalá A, Alonso C, *et al.* A randomized trial comparing chlorambucil plus prednisone vs cyclophosphamide, melphalan and prednisone in the treatment of chronic lymphocytic leukemia stages B and C. *Nouv Rev Fr Hematol* 1988, **30**, 429–432.
49. Jaksic B, Brugiatelli M. High dose chlorambucil for the treatment of B-chronic lymphocytic leukemia (CLL). Update of IGCI CLL trials. *Proc 5th Int Workshop on CLL—Stiges* (Barcelona), 1991, 62.
50. Ezdinli EZ, Stutzman L, Williams Aungst C, Firat D. Corticosteroid therapy for lymphomas and chronic lymphocytic leukemia. *Cancer* 1969, **23**, 300.
51. Keating MJ, Scouros M, Murphy S, *et al.* Multiple agent chemotherapy (POACH) in previously treated and untreated patients with chronic lymphocytic leukemia. *Leukemia* 1988, **2**, 157–164.
52. French Cooperative Group on Chronic Lymphocytic Leukemia. A randomised clinical trial of chlorambucil versus COP in stage B chronic lymphocytic leukemia. *Blood* 1986, **73**, 334.
53. Keating MJ, Hester JP, McCredie KB, Burgess MA, Murphy WK, Freireich EJ. Long-term results of CAP therapy in chronic lymphocytic leukemia. *Leukemia Lymphoma* 1990, **2**, 391–397.
54. Kempin S, Lee BJ, Thaler HT, *et al.* Combination chemotherapy of advanced chronic lymphocytic leukemia: the M-2 protocol (vincristine, BNCU, cyclophosphamide, melphalan and prednisone). *Blood* 1982, **60**, 1110–1121.
55. Spanish Cooperative Group PETHEMA. Treatment of chronic lymphocytic leukemia: a preliminary report of Spanish (PETHEMA) trials. *Leukemia Lymphoma* 1991, **5** (suppl. 1), 89–91.
56. French Cooperative Group on Chronic Lymphocytic Leukemia. Is the CHOP regimen a good treatment for advanced CLL? Results from two randomized trials. *Leukemia Lymphoma* 1994, **13**, 449–456.
57. French Cooperative Group on Chronic Lymphocytic Leukemia. Effectiveness of 'CHOP' regimen in advanced untreated chronic lymphocytic leukemia. *Lancet* 1986, **1**, 1346–1349.
58. French Cooperative Group on Chronic Lymphocytic Leukemia. Long-term results of the CHOP regimen in stage C chronic lymphocytic leukemia. *Br J Haematol* 1989, **73**, 334–340.
59. Majudmar G, Singh AK. Role of splenectomy in chronic lymphocytic leukaemia with massive splenomegaly and cytopenia. *Leukemia Lymphoma* 1992, **7**, 131–134.
60. Rubin P, Bennett JM, Begg C, Bozdech MJ, Silber R. The comparison of total body irradiation vs chlorambucil and prednisone for remission induction of active chronic lymphocytic leukemia: an ECOG study. Part I: total body irradiation: response and toxicity. *Int J Radiat Oncol Biol Phys* 1981, **7**, 1623–1632.
61. Jacobs P, King HS. A randomized prospective comparison of chemotherapy to total body irradiation as initial treatment for the indolent lymphoproliferative diseases. *Blood* 1987, **69**,1642–1646.
62. Juliusson G. Immunological and genetic abnormalities in chronic lymphocytic leukaemia. Impact of the purine analogues. *Drugs* 1994, **47** (suppl. 6), 19–29.
63. Keating MJ. Immunosuppression with purine analogues—the flip side of the gold coin. *Ann Oncol* 1993,**4**, 347–348 (editorial).
64. Bergmann L, Fenchel K, Jahn B, Mitrou PS, Hoezler D. Immunosuppressive effects and clinical response of fludarabine in refractory chronic lymphocytic leukemia. *Ann Oncol* 1993, **4**, 371–375.
65. Larson DL, Tomlinson LJ. Quantitative antibody studies in man. III. Antibody response in leukemia and other malignant lymphoma. *J Clin Invest* 1953, **32**, 317.
66. Bunch C. The co-operative group for the study of immunoglobulin in chronic lymphocytic leukemia. *N Engl J Med* 1988, **319**, 902–907.
67. Plunkett W, Benhamin RS, Keating MJ, Freireich EJ. Modulation of 9-β-D-arabinofuranosyladenine 5′-triphosphate and deoxyadenosine triphosphate in leukemic cells by 2′-deoxycoformycin during therapy with 9-β-D-arabinofuranosyladenine. *Cancer Res* 1982, **42**, 2092–2096.
68. Griffig J, Koob R, Blakley RL. Mechanisms of inhibition of DNA synthesis by 2-chlorodeoxyadenosine in human lymphoblastoid cells. *Cancer Res* 1989, **49**, 6923–6928.
69. Huang P, Chubb S, Plunkett W. Termination of DNA synthesis by 9-β-D-arabinofuranosyl-2-fluoroadenine. A mechanism for cytotoxicity. *J Biol Chem* 1990, **265**, 16617–16625.
70. Parker W, Cheng Y-C. Inhibition of DNA primase by nucleoside triphosphates and their arabinofuranosyl analogues. *Mol Pharmacol* 1987, **31**, 146–151.
71. Spriggs D, Robbins G, Mitchell T, Kufe D. Incorporation of 9-β-D-arabinofuranosyl-2-fluoroadenine into HL-60 cellular RNA and DNA. *Biochem Pharmacol* 1986, **35**, 247–252.
72. Huang P, Plunkett W. Action of 9-β-D-arabinofuranosyl-2-fluoroadenine on RNA metabolism. *Mol Pharmacol* 1991, **39**, 449–455.
73. Robertson LE, Chubb S, Meyn RE, *et al.* Induction of apoptotic cell death in chronic lymphocytic leukemia by 2′-chlorodeoxyadenosine and 9-β-D-arabinofuranosyl-2-fluoroadenine. *Blood* 1993, **81**, 143–150.
74. Carrera CJ, Piro LD, Saven A, Beutler E, Terai C, Carson DA. 2-chlorodeoxyadenosine chemotherapy triggers programmed cell death in normal and malignant lymphocytes. *Adv Exp Med Biol* 1991, **309A**, 15–18.
75. Hirota Y, Yosioka A, Tanaka S, *et al.* Imbalance of deoxyribonucleoside triphosphates, DNA double strand breaks, and cell death caused by 2-chlorodeoxyadenosine in mouse FM3A cells. *Cancer* 1989, **49**, 915–919.
76. Keating MJ, Kantarjian H, Taplaz M, *et al.* Fludarabine: a new

agent with major activity against chronic lymphocytic leukemia. *Blood* 1989, **74**, 19–25.
77. Keating MJ. Fludarabine phosphate in the treatment of chronic lymphocytic leukemia. *Semin Oncol* 1990, **17** (suppl. 8), 49–62.
78. Puccio CA, Mittleman A, Lichtman SM, *et al.* A loading dose/continuous infusion schedule of fludarabine phosphate in chronic lymphocytic leukemia. *J Clin Oncol* 1991, **9**, 1562–1569.
79. Hiddemann W, Rottman R, Wormann B, *et al.* Treatment of advanced chronic lymphocytic leukemia by fludarabine: results of a clinical phase II study. *Ann Hematol* 1991, **63**, 1–4.
80. Zinzani PL, Lauria F, Rondelli D, *et al.* Fludarabine in patients with advanced and/or resistant B-chronic lymphocytic leukemia. *Eur J Haematol* 1993, **51**, 93–97.
81. Fenchel K, Bergmann L, Wijermans P, *et al.* Clinical results and immunosuppressive effects of fludarabine phosphate in pretreated advanced chronic lymphocytic leukemia and non-Hodgkin's lymphoma (abstract 653). *Br J Haematol* 1994, **87** (suppl. 1), 167.
82. Johnson SA, Hiddemann W, Coiffier B, *et al.* A randomised comparison between fludarabine and cyclophosphamide, adriamycin and prednisone in the treatment of chronic lymphocytic leukemia (CLL) (abstract 661). *Br J Haematol* 1994, **87** (suppl. 1), 169.
83. Kemena A, O'Brien S, Kantarjian H, *et al.* Phase II clinical trial of fludarabine in chronic lymphocytic leukemia on a weekly low-dose schedule. *Leukemia Lymphoma* 1993, **10**, 187–193.
84. Keating MJ, Kantarjian H, O'Brien S, *et al.* Fludarabine: a new agent with marked cytoreductive activity in untreated chronic lymphocytic leukemia. *J Clin Oncol* 1991, **9**, 44–49.
85. Hurst PG, Habib MP, Garewal H, Bluestein M, Padiun M, Greenberg BR. Pulmonary toxicity associated with fludarabine. *Invest New Drugs* 1987, 5, 207–210.
86. O'Brien S, Kantarjian H, Beran M, *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**, 1695–1700.
87. Anaissie E, Kontoyiannis DP, Kantarjian H, *et al.* Listerosis in patients with chronic lymphocytic leukemia who were treated with fludarabine and prednisone. *Ann Intern Med* 1992, **117**, 466–469.
88. Piro LD, Carrera CJ, Beutler E, *et al.* 2-chlorodeoxyadenosine: an effective new agent for the treatment of chronic lymphocytic leukemia. *Blood* 1988, **72**, 1069–1073.
89. Saven A, Carrera CJ, Carson DA, Beutler E, Piro LD. 2-chlorodeoxyadenosine treatment of refractory chronic lymphocytic leukemia. *Leukemia Lymphoma* 1991, 5 (suppl. 1), 133–138.
90. Delannoy A, Ferrant A, Doyen C, *et al.* 2-chlorodeoxyadenosine therapy in advanced chronic lymphocytic leukemia (Abstract 649). *Br J Haematol* 1994, **84** (suppl. 1), 166.
91. Dillman RO, Mick R, McIntyre OR. Pentostatin in chronic lymphocytic leukemia: a phase II trial of cancer and leukemia group B. *J Clin Oncol* 1989, 7, 433–438.
92. Ho AD, Thaler J, Stryckmans P, *et al.* Pentostatin in refractory chronic lymphocytic leukemia: a phase II trial of the European Organization for Research and Treatment of Cancer. *J Natl Cancer Inst* 1990, **82**, 1416–1420.
93. O'Connell MJ, Colgan JP, Oken MM, *et al.* Clinical trials of recombinant leucocyte A interferon as initial therapy for favorable histology non-Hodgkin's lymphomas and chronic lymphocytic leukemia. An Eastern Cooperative Oncology Group pilot study. *J Clin Oncol* 1980, **4**, 128–136.
94. Ziegler-Heitbrock HWL, Schlag R, Fleiger D, *et al.* Favorable response of early stage B CLL patients to treatment with IFN-α_2. *Blood* 1989, **73**, 1426–1430.
95. Rozman C, Montserrat E, Viñolas N, *et al.* Recombinant alpha interferon in the treatment of B chronic lymphocytic leukemia in early stages. *Blood* 1988, **71**, 1295–1298.
96. Pangalis GA, Griva E. Recombinant alfa-2b-interferon therapy in untreated stages A and B chronic lymphocytic leukemia. *Cancer* 1988, **61**, 869–872.
97. McSweeney EN, Giles FJ, Worman CP, *et al.* Recombinant interferon alfa 2a in the treatment of patients with early stage B chronic lymphocytic leukaemia. *Br J Haematol* 1993, **85**, 77–83.
98. Foon KA, Bottino GC, Abrams PG, *et al.* Phase II trial of recombinant leucocyte A interferon in patients with advanced chronic lymphocytic leukemia. *Am J Med* 1985, **78**, 216–220.
99. Pettengel R, Gurney H, Radford JA, *et al.* Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. *Blood* 1992, **80**, 1430–1436.
100. Trillet-Lenoir V, Green J, Manegold C, *et al.* Recombinant granulocyte colony-stimulating factor reduces the infectious complications of cytotoxic chemotherapy. *Eur J Cancer* 1993, **29A**, 319–324.
101. Pettengel R, Gurney H, Radford J, *et al.* A randomised trial of recombinant human granulocyte colony-stimulating factor to preserve dose-intensity in non-Hodgkin's lymphoma. *Proc Am Soc Clin Oncol* 1992, **11**, 319.
102. Steinke B, Manegold C, Freund M, *et al.* G-CSF for treatment intensification in high-grade malignant non-Hodgkin's lymphoma. *Onkologie* 1992, **15**, 46–50.
103. Michallet M, Corront B, Hollard D, *et al.* Allogeneic bone marrow transplantation in chronic lymphocytic leukemia: 17 cases. Report from the EB-MTG. *Bone Marrow Transpl* 1991, 7, 275–279.
104. Michallet M. Allogenic bone marrow transplantation in chronic lymphocytic leukemia: 55 cases (abstract 132). Fifth International Conference on Malignant Lymphoma, Lugano, 9–12 June 1993, 103.
105. Michallet M, Archimbauld E, Juliusson G, *et al.* Autologous transplants in chronic lymphocytic leukemia: report of 11 cases (abstract 671). *Br J Haematol* 1994, **87** (suppl. 1), 172.
106. Rabinowe SN, Soiffer RJ, Gribben JG, *et al.* Autologous and allogeneic bone marrow transplantation for poor prognosis patients with B-cell chronic lymphocytic leukemia. *Blood* 1993, **82**, 1366–1376.
107. Khouri IF, Keating MJ, Vriesendorp HM, *et al.* Autologous and allogeneic bone marrow transplantation for chronic lymphocytic leukemia: preliminary results. *J Clin Oncol* 1994, **12**, 748–758.
108. Rabinowe SN, Grossbard ML, Nadler LM. Innovative treatment strategies for chronic lymphocytic leukemia: monoclonal antibodies, immunoconjugates and bone marrow transplantation. In Cheson BD, ed. *Chronic Lymphocytic Leukemia: Scientific Advances and Clinical Developments*. New York, Marcel Dekker, 1993, 337–367.
109. Flandrin G. Richter's syndrome. In Polliack A, Catovsky D, eds. *Chronic Lymphocytic Leukaemia*. Harwood Academic Publishers, 1988.
110. Foon KA, Thiruvengadam R, Saven A, Bernstein ZP, Gale RP. Genetic relatedness of lymphoid malignancies. Chronic lymphocytic leukemia as a model. *Ann Intern Med* 1993, **119**, 63–73.
111. Catovsky D. Diagnosis and treatment of CLL variants. In Cheson BD, ed. *Chronic Lymphocytic Leukemia. Scientific Advances and Clinical Developments*. New York, Marcel Dekker, 1993, 369–397.
112. Smith OP, Mehta AB. Fludarabine monophosphate for prolymphocytic leukemia. *Lancet* 1990, **336**, 820.
113. Sporn JR. Sustained response of refractory prolymphocytic leukemia to fludarabine. *Acta Haematol* 1991, **85**, 209–211.
114. Marlton P, McCarthy C, Taylor K. Letter to the editor: fludarabine-induced cytogenic remission in prolymphocytic leukemia. *Am J Hematol* 1992, **40**, 71–72.