State-of-the-Art Management of Patients Suffering from Chronic Lymphocytic Leukemia

Ruth Clifford and Anna Schuh
Oxford Cancer and Haematology Centre, Oxford University Hospitals, Churchill Site, Oxford, OX3 7JL, United Kingdom.
Corresponding author email: anna.schuh@ndcls.ox.ac.uk

Abstract: The management of chronic lymphocytic leukemia (CLL) has evolved dramatically in the last decade. For the first time, clinical intervention has been shown to alter the natural history of the disease. Considerable efforts are focussing on better patient selection and response prediction, and it is expected that the publication of the first 200 CLL genomes will spark new insights into risk stratification of CLL patients. Besides, many new agents are being evaluated on their own and in combination therapy in early and late Phase clinical studies. Here, we provide a general clinical introduction into CLL including diagnosis and prognostic markers followed by a summary of the current state-of-the-art treatment. We point to areas of continued clinical research in particular for patients with co-morbidities and highlight the challenges in managing refractory disease.

Keywords: chronic lymphocytic leukemia (CLL), treatment of, clinical trials

doi: 10.4137/CMO.S6201
This article is available from http://www.la-press.com.
© the author(s), publisher and licensee Libertas Academica Ltd.
This is an open access article. Unrestricted non-commercial use is permitted provided the original work is properly cited.
Background
Chronic lymphocytic leukemia (CLL) is the most common adult leukemia. At diagnosis, 85% of patients are older than 65 years of age. Therefore, this leukemia represents a significant challenge for healthcare systems of aging populations. Treatment of CLL has evolved significantly in recent years. In younger patients without co-morbidities, treatment goals have shifted from symptom control to achieving long lasting remissions or even cure. The advent of many new agents, in particular anti-CD20 antibodies, has increased patients’ choice of treatment and improved clinical outcomes. In particular, the addition of rituximab to the chemotherapy backbone has changed the natural history of CLL by improving overall survival. However, many issues remain unresolved: the increasing use of more toxic and expensive therapeutic regimens demands better risk stratification and response prediction. The question of early treatment versus active surveillance has re-emerged as an area of research interest. Whether achieving eradication of minimal residual disease (MRD) should become a treatment goal in younger patients and what the role of maintenance treatment should be remains unknown.

The third part of the review deals with some of the novel therapies currently under investigation.

Molecular Pathogenesis in CLL
It is generally accepted that CLL derives from antigen experienced mature B cells homing to secondary lymphoid organs. Defects in the cell death machinery combined with the contribution from the stromal microenvironment and accessory cells lead to expansion of an abnormal lymphoid cell population. Antigenic input and B cell receptor (BCR) signaling play an important role in this process.

The BCR is the key survival molecule for normal and malignant B cells. Following antigen engagement of BCR, activation of intracellular protein kinases occurs which allows secondary downstream signaling involving pathways such as PI3K/AKT/mTOR, ultimately mediating changes in cell proliferation and cell survival. Inhibition of BCR signalling is therefore an important mechanism of controlling the proliferation and survival of CLL cells.

Prolonged survival of malignant B cells is a feature of CLL thought to result from an imbalance between pro- and anti-apoptotic members of the Bcl-2 family. As Bcl-2 is overexpressed in CLL cells this is another area of active drug development. Finally it is thought that soluble factors such as cytokines, stromal cells, T cells and nurse like cells are involved in maintaining the CLL cell’s viability within the bone marrow or lymph node and allowing development of drug resistance. Disruption of this microenvironment and removal of these protective stimuli may lead to CLL cell death. We will discuss treatments targeting these pathobiological processes in more detail below.

Diagnosis and Staging
CLL is a heterogenous disease with a wide variability in disease presentation and course. While some patients with CLL will never require therapeutic intervention, many others require multiple lines of chemotherapy and often die from the disease. Current guidelines outline diagnosis and staging of CLL based on the characteristic immunophenotype of CD19 and CD5 positivity present on $5 \times 10^9/L$ peripheral blood B lymphocytes. The iwCLL guidelines recommend disease assessment using Rai or Binet Staging systems to guide treatment initiation as these provide a reliable prediction of a patient’s prognosis based solely on physical examination and blood counts.

Prognosis
A variety of prognostic biomarkers have been studied in CLL. Analysis of somatic mutations of the immunoglobulin heavy chain variable (IGHV) region is used to stratify CLL patients into two distinct biological and prognostic groups on the basis of whether the IGHV genes are hypermutated (<98% homology with germline) or unmutated (>=98% homology). As this is a difficult and expensive test to perform routinely in clinical laboratories, surrogate...
markers such as zeta associated protein 70 (ZAP70) and CD38 expression have been evaluated.\textsuperscript{12–15} The use of a combination of both CD38 expression and ZAP70 can classify CLL patients into 2 risk groups with a double negative result equating to an excellent prognosis and double positive a poor prognosis.\textsuperscript{16}

Cytogenetic abnormalities are detected in approximately 80% of CLL patients using interphase fluorescence in situ hybridisation (FISH).\textsuperscript{17} Dohner et al investigated 325 mainly untreated CLL patients and identified five prognostic categories. Of these, patients with 17p deletions and 11q deletions had the worst outcome. The median treatment-free interval for these groups was 9 and 13 months, respectively. More recently, it has been shown that the addition of rituximab to standard chemotherapy may overcome the adverse prognostic significance of 11q deletions but not of del17p.\textsuperscript{18,19}

Mono- or bi-allelic mutations of TP53 without del17p also confer a poor prognosis and chemotherapy refractoriness. Del17p/TP53 abnormalities occur in about 8% of patients at diagnosis and 25% of fludarabine refractory cases.\textsuperscript{20,21} It is therefore recommended to test for deletions and/or mutations of TP53 before each course of treatment.

**Response Prediction Using Whole Genome Approaches**

As outlined in more detail below, treatment of patients with CLL has evolved in recent years and many patients are exposed to potentially more toxic agents like purine analogues or alemtuzumab. Besides, modern chemo-immunotherapy is significantly more expensive than single agent chlorambucil. There is therefore an urgent need to identify responders and non-responders early in order to avoid inappropriate drug use leading to unnecessary side-effects and expense. Advances in whole genome array and sequencing technology will likely transform response prediction over the next decade by allowing us to identify genetic markers which can direct treatment choice.

Copy number alterations (CNAs), which are deletions or amplifications of chromosomal material, or uniparental disomy, can be revealed by high-resolution genome-wide arrays. Genomic complexity is defined by the presence of more than 3 CNAs or a total length of CNAs of >5 megabases and has been shown to correlate with disease progression, clonal evolution and refractory disease in CLL.\textsuperscript{22,23} Our own data on paired pre-treatment and relapse samples extends these analyses by showing that the complexity of CNAs increases over time in the same patient and pinpoints to candidate drivers of disease progression.\textsuperscript{24} Whole genome sequencing (WGS) and whole exome sequencing (WES) of 200 patients and their germline controls, has revealed a complex mutation spectrum in CLL, mirroring its clinical and biological heterogeneity.\textsuperscript{25–27} Recurrent gain-of-function mutations in Notch1 were found in 12% of CLL patients, with a higher proportion found in chemotherapy-refractory CLL and during progression to Richter’s transformation. These findings are supported by two further studies associating Notch1 mutations with clinically aggressive CLL.\textsuperscript{28,29} Importantly, although Notch1 mutated patients lacked TP53 disruption in >90% of cases, the overall survival (OS) predicted by Notch1 mutations was similar to that of TP53 mutated/deleted CLL. Mutations in the splicing factor SF3B1 are present in ∼10% of CLL patients and also predict poor prognosis.\textsuperscript{26,30} However, most mutations identified by genome-wide sequencing are non-recurrent or recurrent at low frequency. While the results of these novel technologies are unravelling the pathobiological processes in CLL, prospective validation of their clinical significance is required prior to implementation in clinical practice.

**Treatment**

**General principles**

**When to treat?**

The treatment of CLL poses many challenges, not least to convey to patients that no treatment is indicated for their newly diagnosed leukaemia. that no treatment is indicated. Although treatment indications have been clearly defined,\textsuperscript{2} the exact time when treatment should be initiated can be subjective and dependent more on severity of symptoms then objective criteria. In discussions with patients and relatives, the patient’s preference should be taken into consideration whenever possible, as CLL is a chronic cancerous condition that patients live with for years. A meta-analysis of initial studies using chlorambucil with or without prednisolone did not show any benefit for early treatment versus watch and wait.\textsuperscript{31} This question is currently being revisited by the German CLL Study Group using modern chemoimmunotherapy versus watch and wait in high-risk disease.
Aims of treatment

Only 15% of patients diagnosed with CLL are under the age of 65. On the other hand, 66% of patients recruited into the German CLL trials were younger than 64 (Goede, IX AROSA Workshop 2004). Similar recruitment figures are found around the world. Western societies are confronted with a rise in the elderly population and an improvement in life expectancy. There is therefore a clinical need to design specific treatments for older patients who often have multiple co-morbidities. It is critical to define the goals of therapeutic intervention from the outset together with patients and their families.

Apart from prolonging life to the predicted life expectancy of an individual, treatment of elderly patients with cancer should aim to improve or maintain quality of life. Although age is a helpful indicator of what the treatment goal should be, there is a considerable grey area in patients between 55 and 70 years of age. A patient’s performance status rather than their chronological age can be more informative. Scoring systems such as the Cumulative Illness Rating Scale (CIRS) to establish and quantify co-morbidities have been validated in the elderly and are being used as part of clinical trials. Their value in day-to-day clinical practice is less clear. The GCLLSG utilises this scoring system to stratify patients based on CIRS score; ‘Go-Go’ patients have a low co-morbidity score and a normal creatinine clearance, and ‘Slow-Go’ patients have relevant comorbidities.

On the other hand, in young patients without co-morbidities (Go-Go), curative options should at least be considered.

Intimately linked to these considerations is the desired depth of response. There is clear evidence that minimal residual disease (MRD) eradication is associated with a better overall survival as well as progression free survival (PFS) providing a clear rationale for using the most effective treatment available up-front. This is also corroborated by emerging long term follow up data suggesting that sequential treatment with chlorambucil followed by fludarabine shortens OS compared to fludarabine treatment up-front, and therefore implying that the

Figure 1. Flow diagram of proposed treatment algorithm for CLL.

Abbreviations: W and W, watch and wait; FCR, fludarabine cyclophosphamide rituximab; Clb, chlorambucil; PFS, progression free survival; BMT, bone marrow transplantation.
most effective treatment should be given preference. However, whether eradication of MRD should become a treatment goal and obtained with maintenance treatment remains an area of active research.\textsuperscript{37}

The treatment algorithm proposed in this review is summarized in Figure 1. A summary of pivotal clinical trials defining treatment for patients with CLL is given in Table 1.

Table 1. Summary of pivotal Phase II/Phase III trial in CLL.

| 1st line treatment | Reference | Median age | Patient numbers | Results |
|--------------------|-----------|------------|-----------------|---------|
| **GO-GO patients** |           |            |                 |         |
| FC v F v Clb       | Catovsky LRF CLL4\textsuperscript{36} | 65          | 777             | CR: 35% v 7% (P < 0.001) ORR: 94% v 80% (P < 0.001) v 72% PFS at 5 years: 36% v 10% v 10% (P < 0.001) |
| F v Clb            | Rai\textsuperscript{79} | 64          | 350             | CR: 20% v 4% (P < 0.001) ORR: 63% v 37% (P < 0.001) PFS median: 20 v 14 months (P < 0.001) |
| FCR v FC           | Hallek\textsuperscript{40} | 61          | 817             | CR: 44% v 22% (P < 0.0001) ORR: 90 v 80% (P < 0.0001) 3 yr PFS: 65% v 45% (P < 0.001) OS: 87% v 83% (P = 0.01) |
| **SLOW-GO patients** |           |            |                 |         |
| Bendamustine vs Clb| Knauf\textsuperscript{65} | 63          | 319             | CR: 31% v 2% ORR: 68% v 31% (P < 0.0001) PFS median: 21.6 v 8.3 months (P < 0.0001) |
| F v Clb            | Eichhorst\textsuperscript{63} | 70          |                 | ORR: 72% v 51% (P = 0.003) CR: 7% v 0% (P = 0.011) PFS: 19 v 18 months (P = 0.7) |
| **Relapse treatment** |           |            |                 |         |
| GO-GO patients     |           |            |                 |         |
| FCR v FC           | Robak\textsuperscript{41} | 63          | 552             | CR: 24.3% v 13% (P < 0.001) ORR: 69.6% v 58% (P = 0.0034) PFS median: 30.6 v 20.6 months (P < 0.001) OS median: 46 v 64 months (P = 0.15) |
| **SLOW-GO patients** |           |            |                 |         |
| **High risk patients** |           |            |                 |         |
| GO-GO patients     |           |            |                 |         |
| Alemtuzumab S/C    | Stilgenbauer CLL2H study\textsuperscript{20} | 63          | 103             | CR 4% ORR 34% PFS median: 7.7 months OS median: 19.1 months |
| Alemtuzumab        | Pettitt\textsuperscript{45} | 56          | 52              | CR: 36% ORR: 85% PFS: 11.8 months OS: 23.5 months |
| Prednisolone       |           |            |                 |         |
| CFAR               | Parikh\textsuperscript{46} | 59          | 60              | CR: 70% (14 patients w p53 del – CR 57%) ORR: 92% PFS median: 33 months |
| SLOW-GO patients   | Ofatumumab | Wierda\textsuperscript{68} | 63          | 138             | CR: 0% ORR: 53% PFS median: 5.8 months OS median: 14.5 months |
Go-Go
1st line treatment
Over the last decade, considerable progress has been made in the treatment of physically fit patients with CLL. Purine-analogue combinations have improved treatment outcomes. Importantly, we have witnessed a paradigm shift in the management of CLL changing for the first time the natural history of the disease. The German CLL8 study compared FC versus FCR and demonstrated that therapeutic intervention in CLL led to an improved overall survival in patients with CIRS scores of <6. There was no upper age limit for this study, but the median age was 61 years. Only 10% of patients were ≥70 years old. Overall response rates (ORR) were 80% vs 90% for FC and FCR, respectively. At 3 years after randomisation, 65% of patients in the chemotherapy group were free of progression compared with 45% in the chemotherapy group (hazard ratio: 0.56; 95% CI 0.46–0.69, \( P < 0.0001 \)); 87% were alive versus 83%, respectively (0.67 [0.48–0.92]; \( P = 0.01 \)). Patients with del11q benefitted particularly from the addition of rituximab. On the other hand, neither FC nor FCR were effective at treating patients with del17p. Following the publication of this study, FCR is considered the new standard of care for fit patients with CLL in first line treatment.

Relapse treatment
FCR combination treatment is also effective in the relapse setting. The REACH study included patients at first relapse. However, the majority of patients in the study had previously received chlorambucil and were rituximab naïve. After a median follow-up time of 25 months, rituximab significantly improved progression-free survival (PFS) in patients with previously treated CLL (hazard ratio: 0.65; \( P \) value < 0.001; median PFS: 30.6 months for R-FC vs 20.6 months for FC). Relapse data on patients previously treated with FCR is emerging. In a single centre study, 33 of 112 patients who relapsed after initial treatment with FCR were retreated with FCR. Patients who relapsed after 3 years had an ORR and CR of 86% and 23% compared to 54% and 0% for those relapsing within 3 years. On the basis of these data, FCR has therefore become the standard relapse treatment for GO-GO patients. However, there is still some debate around the definition of FCR refractoriness. Bearing in mind side-effects from FCR and its cost, it is reasonable to assume that re-treatment with FCR should only be attempted if the PFS after first line FCR is more than 2 years.

Patients with del17p/TP53 mutation and purine analogue refractory patients
Patients with deletions of chromosome 17p or TP53 mutation or purine analogue refractory disease have a poor prognosis and usually show only limited response to salvage chemotherapy. Alternative treatments are therefore urgently required. Subcutaneous administration of alemtuzumab is as effective and safe as intravenous administration with response rates ranging between 22% and 34% and median overall survival times between 10 and 19 months. Despite the absence of randomised studies, it has become the “standard of care” for patients with TP53 deleted/mutated or purine analogue refractory disease. Alemtuzumab is not effective in patients with bulky lymphadenopathy. Combination treatment with high dose steroids, in particular high dose methylprednisolone (1 g/m²/d × 5 days) or pulsed dexamethasone (40 mg/d × 4 days every 14 days), is therefore being evaluated. An initial Phase 2 study showed improved ORR and CR rates of 85% and 36%, respectively, and a median PFS and OS of 11.8 months and 23.5 months.

Further intensification has been achieved by combining alemtuzumab to FCR treatment (CFAR regimen). Using CFAR, patients with high-risk CLL achieved ORR of 92% and CR rates of 70% in first line. However, combinations of alemtuzumab with fludarabine are not recommended outside clinical trials due to the increased rate of fatal infectious episodes.

Allogeneic transplantation
For younger patients without co-morbidities and high-risk CLL, bone marrow transplantation to consolidate remission should be considered. High risk CLL was defined by the EBMT CLL transplant consensus as:

- Non-response or early relapse (within 12 months) after purine analogue-containing therapy
State-of-the-art in CLL

- Relapse (within 24 months) after purine analogue combination therapy or treatment of similar efficacy (ie, autologous stem cell transplantation)
- del17p/TP53 deletion/mutation requiring treatment

An EBMT retrospective study of 44 transplants performed between 1995 and 2006 for del17p CLL showed that about one third of patients achieved long-term remission. A retrospective case control study suggested a survival advantage for patients with high risk CLL treated with reduced intensity conditioning (RIC) BMT.

Data from Seattle on 82 patients undergoing RIC-allografting quotes 5-year incidences of non-relapse mortality (NRM), progression/relapse, overall survival, and progression-free survival of 23%, 38%, 50%, and 39%, respectively. In this study, a lymph node size of >/= 5cm, but not cytogenetic abnormalities, was associated with outcome. In the GCLLSG CLL3X trial, the 4-year EFS after RIC-allo BMT was 42% and similar for all genetic subtypes, indicating that del17p loses its adverse prognostic significance in this therapeutic context.

Overall, outcome data from conventional BMT and RIC allo-BMT demonstrate a higher TRM in CLL compared to other diseases. The reasons for this are poorly understood, but might be related to the increased age, secondary immunodeficiency and possibly to the T-cell depleting induction treatment. Autologous PBSCT are not performed in CLL due to the high risk of MDS/AML and the lack of overall survival benefit despite improved PFS and EFS.

Maintenance

The observation that MRD negative remissions are associated with prolonged PFS both in previously untreated and relapsed cases has led to studies of additional treatment in patients with residual disease after induction therapy.

The use of alemtuzumab following initial therapy with fludarabine-based regimens has improved CR rates, led to MRD eradication and prolonged PFS. An initial Phase 3 trial revealed ORR of 46% with clearance of MRD in 11 of 29 patients. The GCLLSG randomised patients to receive alemtuzumab consolidation or no treatment after first-line fludarabine +/- cyclophosphamide treatment. Out of 22 evaluable patients, 11 of whom had alemtuzumab, the median PFS at 48 months was significantly improved in the treatment arm (not reached versus 20.6 months, \( P = 0.004 \)). However infectious complication rates necessitated early closure of this trial. A further Phase 2 trial evaluated subcutaneous alemtuzumab in the consolidation setting. Of the 29 evaluable patients, 23 had a response. The majority of treatment related adverse events were grade 1/2 and four patients experienced serious infections. Careful attention to the timing of consolidation therapy and to antimicrobial prophylaxis and treatment is warranted.

Preliminary data suggest that consolidation therapy with rituximab may also prolong PFS. Foon et al combined a lower dose of fludarabine and cyclophosphamide (20 mg/m² and 150 mg/m², respectively, \( \times 3 \) days every 4 weeks) with standard dose rituximab (500 mg/m² every 14 days) including rituximab maintenance every 3 months until relapse (FCR-Lite).

Complete responses were seen in 77% of patients, none of whom had relapsed at a median follow up time of 22.3 months. Among the 11 PRs, nine patients progressed and 5 died from CLL-related complication. The impact of maintenance therapy in this trial is yet to be realised. The Spanish CLL Study Group recently presented the final results of a Phase 2 clinical trial evaluating rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) followed by rituximab maintenance for front-line treatment of CLL. Patients achieving a CR or PR after 6 cycles of R-FCM received rituximab maintenance every 3 months (375 mg/m²) for 2 years. 64 patients completed 4 cycles of maintenance and were evaluable for a response. Neutropenia was observed in 31% of patients and 16 patients experienced grade 3/4 infectious complications. There were 2 deaths, one from multifocal leukoencephalopathy and one from hemophagocytic syndrome. Among 35 patients in MRD-negative CR after R-FCM induction, 22 maintained the MRD-negative status, 9 (25.7%) switched from MRD-negative to MRD-positive, and 4 failed treatment. Median time to conversion from negative to positive MRD was 45.4 months, which is significantly longer compared to FCM only treated patients (45.4 vs. 16.4 months; \( P = 0.011 \)). This maintenance regime shows activity in CLL and may improve outcomes by impacting on MRD negativity, however this benefit needs to be tempered by the toxicity profile.
Slow-Go
There is currently no standard of care for patients with CLL older than 70 years of age or patients with co-morbidities.

1st line treatment
Chlorambucil has been in use for the past 40 years.31 Approximately 70% of 1st line patients are expected to obtain a response to chlorambucil. However, complete remissions are rare and the mean PFS is 18 months.38 More recently, chlorambucil was combined with rituximab in an open label Phase II study.62 Across trial comparison of response rates would suggest that this regimen might induce more responses (ORR: 84%) and a longer PFS.

The use of purine analogues in the elderly remains an area of active research. Only 10% of patients in the German CLL8 study were over the age of 70 and none had CIRS scores of >6. Besides, there is no overall survival benefit for elderly patients treated with fludarabine versus chlorambucil.63 Bendamustine, a purine analogue-alkylator hybrid used in Eastern Germany for the past 40 years, compared favourably to chlorambucil in a frontline study for elderly patients.65 However, for reasons not entirely understood, results in the chlorambucil control arm were significantly worse in this study compared to the UK CLL4 trial. Bendamustine was well tolerated with little myelotoxicity. As it is metabolised by the liver, it is of particular benefit in patients with renal impairment.

Relapse treatment
Patients with PFS of over one year can be re-treated with 1st line single agent chemotherapy. Bendamustine, in combination with rituximab, also showed significant activity in relapsed/refractory patients.66 In this study, 37% of patients were over the age of 70 and 42% had a creatinine clearance of <70 ml/min. 60% of patients experienced at least one Grade 3–4 adverse events during the course of treatment. The ORR was 59% and the median PFS was 15 months. Patients with del17p and fludarabine refractory patients benefitted least from BR treatment. The bendamustine and rituximab combination is being taken forward by the German CLL study group in a direct head to head comparison with FCR in GO-GO patients.

Refractory elderly patients
Refractory disease in older patients and patients with co-morbidities, who are not eligible for BMT, represents one of the major challenges ahead. Refractory treatments such as alemtuzumab and high dose methylprednisolone are used, but often with considerable side-effects.

Second generation monoclonal anti-CD20 antibodies represent an attractive alternative for this group of patients. Ofatumumab, a fully humanised second-generation anti-CD20 antibody has proven efficacy in relapsed CLL. In an initial Phase 1/2 study Coiffier et al enrolled 33 relapsed CLL patients and achieved a 50% ORR.67 The drug obtained accelerated FDA approval for treatment of fludarabine and alemtuzumab refractory (FA-ref) disease subsequent to the pivotal phase II study on 138 patients with either FA-ref or bulky fludarabine refractory (BF-ref) disease. This study showed a 55% overall response rate which compared favourably to the expected 15%.68 Median progression-free survival and overall survival times were 5.7 and 13.7 months in the FA-ref group, respectively, and 5.9 and 15.4 months in the BF-ref group, respectively. Interestingly, a subsequent subgroup analysis showed that response to ofatumumab was independent from previous rituximab treatment and rituximab refractoriness.69,70

Novel Therapies, Therapies Under Development
As conventional chemotherapy regimes are toxic thus limiting their application in many elderly CLL patients, and high risk CLL patients have limited responses to current treatment options, novel treatment strategies are required. Molecular targeted treatments that by pass resistance mechanisms to cytotoxic drugs are particularly desirable.

More recently, a number of relevant signals down-stream of the BCR or BCR co-stimulatory molecules, have been implicated in CLL. Inhibitors to the BCR signaling pathway, agents directed at re-activating the death pathways and immunomodulatory agents have all shown promising activity in early phase studies.

Novel anti-CD20 antibodies
A plethora of therapeutic monoclonal antibodies are currently undergoing pre-clinical and clinical
evaluation. GA101 is well tolerated and, like ofatumumab, is significantly more potent and effective in depleting B cells than rituximab in preclinical models. In a Phase I study of 13 heavily pretreated CLL patients, GA101 had a similar safety profile to that observed in Non-Hodgkins Lymphoma patients and had an ORR of 62%. Phase II trials are currently ongoing.

**Lenalidomide**

Lenalidomide, an immunomodulatory drug with more potent activity than thalidomide, has shown tolerability and efficacy in relapsed refractory CLL patients. Ferrajolis et al studied 44 patients who had received an average of 5 previous treatments. Following lenalidomide, the ORR was 32% with CR rates of 3%, however 6 to 9 months were needed to achieve optimal response. Based on these promising results in a heavily pretreated population, upfront treatment with lenalidomide was evaluated in 2 further studies. Following initial toxic events of sepsis and tumour lysis in the first 2 patients enrolled, the protocol was changed to a more conservative dosing schedule (median dose of 10 mg od) including dose escalation. Badoux et al recently published their results on 60 previously untreated CLL patients aged 65 or over. After a median follow up of 29 months, 88% patients are alive and 53% remain on treatment with an estimated 2-year PFS of 60% (95% CI, 46%–72%). An ORR of 65% with a 10% CR rate was achieved. Serious infections or neutropenia of Grade 3 were noted in 13% of patients with one fatal infection. Patients with 17p deletion identified by FISH (n = 6) were less likely to achieve a response (P = 0.001). Trials combining lenalidomide with rituximab or fludarabine and rituximab and the evaluation of low-dose lenalidomide in the maintenance setting are still in progress.

**Flavopiridol**

Flavopiridol, an inhibitor of cyclin-dependent kinases, shows activity in CLL patients including high-risk groups with 17p deletions. Lin et al evaluated 64 patients with a median age of 60 years and a median of 4 prior therapies in a Phase II trial of single-agent flavopiridol. 34 patients achieved a response (53%) including 57% and 50% of patients with del17p or del11q, respectively. Median progression free survival was 10 to 12 months across all cytogenetic risk groups. Tumour lysis syndrome was a significant dose-limiting toxicity and subsequent trials will amend the dosing schedule based on these results.

**Inhibitors of B-cell receptor signalling**

B cell receptor signaling influences disease progression in CLL and many small molecule inhibitors targeting various downstream signalling pathways are under investigation. Promising clinical responses have been observed with fostamatinib disodium (FosD), a SYK inhibitor; PCI-32765, a Bruton tyrosine kinase inhibitor; and CAL-101, a selective inhibitor of PI3K. These drugs are available in oral preparations and are given as continuous treatment. Initial rapid resolution of lymphadenopathy is accompanied by a transient rebound lymphocytosis. After a number of months of continuous therapy remissions can be achieved in a substantial number of patients. Further preclinical and clinical series are needed to outline toxicities, efficacy and potential drug combinations in CLL patients. BCR inhibitors are currently being evaluated in relapsed patients in combination with bendamustine and/or rituximab.

**Bcl-2 antagonists**

Bcl-2 is known to have anti-apoptotic functions and is over-expressed in many lymphoid malignancies including CLL. Oblimersen, a Bcl-2 antisense molecule has shown activity in relapsed CLL patients. A phase III study randomised 241 relapsed CLL patients to receive fludarabine and cyclophosphamide, with or without oblimersen. The rate of CR plus nodular PR in the oblimersen group versus FC alone was 17% compared with 7%. Obatoclax is a small molecule pan-Bcl-2 inhibitor which has shown promising clinical activity in relapsed CLL. Neurological toxicity of unclear aetiology was a manageable side effect. A phase III study in combination with FCR is planned. An orally bioavailable BH3 mimetic, Navitoclax, inhibits several of the Bcl-2 family members and is active in CLL. Recently, it has been reported that combining this agent with FCR or BR in relapsed CLL patients has anti-tumour activity and is well tolerated. In the BR arm the ORR was 81% (13/16) including responses in TP53 deleted patients.
The most common grade 3/4 adverse events were thrombocytopaenia and neutropaenia. Further results from this trial are awaited.

**Complications**

**Infections**

Prevention and treatment of disease complications should be the focus of attention when seeing patients in follow-up clinics. Annual influenza vaccination and vaccinations against encapsulated bacteria should be considered, especially early on in the disease when secondary immunodeficiency has not yet developed and patients are more likely to mount immune responses. Patients with bronchiectasis or chronic infections might be considered for antibiotic prophylaxis or intravenous immunoglobulins. Atypical infections with pneumocystis jirovecii, listeria, mycobacteria, CMV re-activation, Herpes simplex and Herpes zoster should be part of the differential diagnosis especially in pre-treated patients.

**Autoimmune complications**

Patients with CLL present with a range of autoimmune complications, most commonly autoimmune haemolytic anaemia and idiopathic thrombocytopaenia purpura. These can be controlled with steroids in two thirds of patients. Second line therapies include rituximab, splenectomy, alemtuzumab or steroid sparing agents such as cyclosporine. Treatment of the underlying CLL should be considered if appropriate. Other immune-complications have been described and patients with CLL can have paraproteins and cryoglobulins.

**Richter’s syndrome**

Richter’s Syndrome (RS) is a rare complication of CLL, occurring in about 2.2%–15% of patients depending on the series. The underlying pathology can be a diffuse large B-cell lymphoma (DLBCL) or rarely Hodgkin’s disease. Patients with RS typically present with a history of CLL, severe B symptoms, elevated lactate dehydrogenase levels, and rapidly enlarging lymph nodes. Diagnosis is confirmed by biopsy of an enlarging lymph node or other involved site. RS is intrinsically more chemo-resistant than de novo DLBCL, and displays high-risk genomic aberrations, such as del17p and TP53 mutations, that render these disorders refractory to conventional regimens. Extensive disease involvement, high tumour burden and rapid disease kinetics are common features of RS affecting up to 50% of cases. In addition, tumour burden is an independent predictor of poor survival in RS patients. Patient frailty because of poor performance status, poor bone marrow function or immunodeficiency is a common feature in the context of RS, and represents an independent predictor of poor survival after transformation.

The frailty of RS patients precludes the use of high dose chemotherapy with stem cell rescue in a substantial fraction of patients, thus limiting the therapeutic options and the possible benefit derived from myeloablative regimens. Management of Richter’s syndrome therefore remains unsatisfactory with overall response rates of around 34% using CHOP or platinum containing chemotherapy, and 47% using rituximab-containing regimen. The mean overall survival is around 8 months from end of treatment. Responses to ABVD in cases of Hodgkin’s transformation are barely any better. This has led investigators to test several other experimental regimens.

In particular, the hyper-CVXD regimen (dexamethasone, cyclophosphamide, vincristine, doxorubicin, cytarabine) induced a response in 41% of patients with RS (CR rate of 38%), with a median overall survival duration of 10 months. When compared with hyper-CVXD alone, hyper-CVXD plus rituximab and GM-CSF alternating with methotrexate and cytarabine plus rituximab and GM-CSF did not appear to improve the rates of response, disease recurrence-free survival, or overall survival. Both regimens had comparable toxicity, which included neutropenia, thrombocytopenia, and infectious complications.

The combination of fludarabine, cytarabine, cyclophosphamide, cisplatin, and GM-CSF (FACPGM) has been reported to have limited activity and significant toxicity in RS. In a Phase II study, FACPGM was administered to 22 patients with RS or refractory PLL or NHL. FACPGM induced a CR in 1 of 16 patients (6%) with RS.

A single centre Phase I-II study run at the MD Anderson using OFAR (Oxaliplatin, Fludarabine, Ara-C and Rituximab), not specifically aimed at patients with Richter’s Syndrome, also included patients with chemotherapy refractory CLL. OFAR was given in 4 weekly cycles. The main aim of the study was to evaluate the role of
State-of-the-art in CLL

platinum-containing regimen in refractory CLL. There was no maintenance treatment. The 20 patients with Richter’s syndrome had an overall response rate of 50% and a response duration of 10 months, ie, similar to the historic controls of CHOP-R but with added toxicity.

Allogeneic stem cell transplantation might be a promising therapeutic strategy for patients with RS who are fit enough to tolerate transplant related toxicities. Eight patients were treated with high-dose chemotherapy followed by an allogeneic stem cell transplant. Five patients were in resistant relapse and three others were in sensitive or untreated relapse of RS. The median number of previous therapies was 4 (range, 2–5 therapies). Six patients received the transplant from an HLA-identical sibling and two patients received the transplant from an unrelated donor. Three patients (38%) achieved durable disease remissions and were free of disease at 14 months, 47 months, and 67 months, including 2 patients who received non-myeloablative preparative regimens. Five patients died of treatment-related toxicities (3 patients within 30 days of transplantation). According to a non-randomized comparison of two RS cohorts, the estimated cumulative survival at 3 years has been reported to be 75% for patients who received allogeneic SCT after a CR, CRu or PR, compared to 27% for patients who responded to initial therapy but received no allogeneic SCT. Remarkably, allogeneic SCT has no benefit in RS patients who are refractory to induction regimens.

In view of the poor prognosis of Richter’s Syndrome, patients should be entered into clinical trials whenever possible. The UKCLL NCRN group is currently recruiting into a Phase II study (CHOP-OR) using ofatumumab in induction in combination with CHOP followed by ofatumumab maintenance for one year.

Perspective
CLL treatment has changed dramatically in the past decade and thanks to chemo-immunotherapy remission durations of several years with improvement in overall survival have been achieved. However, not all patients benefit from current treatment strategies. Future efforts have to focus on evaluating the plethora of new anti-cancer agents now available for tolerability in older patients with co-morbidities. Their efficacy has to be assessed after genetically informed risk stratification and response prediction that directs targeted therapies to the right patient. In view of their favourable safety profile, the combination of antibodies with BCR inhibitors might represent an attractive and tangible option for these patients. In the longer term, the recent WGS and WES data have revealed novel pathways of relevance in CLL such as Notch1 and the spliceosome. Inhibitors of these pathways are already undergoing pre-clinical and early clinical evaluation. Besides, we need to establish complementary ways of assessing response by focussing on quality of life and activities of daily living (ADL) assessments in addition to survival curves. We hope that in future, these personalized approaches will further improve outcomes and maybe even cure patients with CLL.

Acknowledgements
This work was supported by the Oxford Partnership Comprehensive Biomedical Research Centre with funding from the Department of Health’s NIHR Biomedical Research Centres funding scheme. The views expressed in this publication are those of the authors and not necessarily those of the Department of Health.

Author Contributions
Wrote the first draft of the manuscript: RC. Contributed to the writing of the manuscript: AS. Agree with manuscript results and conclusions: AS. Jointly developed the structure and arguments for the paper: RC and AS. Made critical revisions and approved final version: AS. All authors reviewed and approved of the final manuscript.

Funding
This work was supported by the Oxford Partnership Comprehensive Biomedical Research Centre with funding from the Department of Health’s NIHR Biomedical Research Centres funding scheme. The views expressed in this publication are those of the authors and not necessarily those of the Department of Health.

Competing Interests
Anna Schuh receives honoraria and an unrestricted educational grant from GSK.
Disclosures and Ethics
As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

References
1. Altekruse SF, KC, Krapcho M, Neyman N, et al. SEER Cancer Statistics Review. 1975–2009, National Cancer Institute. Bethesda, MD, 2010. seer.cancer.gov/csr.
2. Hallek M, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446–56.
3. Oscier D, et al. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. Br J Haematol. 2004;125(3):294–317.
4. Stevenson FK, et al. B-cell receptor signaling in chronic lymphocytic leukemia. Blood. 2011;118(6):4313–20.
5. Capitani N, Baldari CT. The Bcl-2 family as a rational target for the treatment of B-cell chronic lymphocytic leukaemia. Curr Med Chem. 2010;17(9):801–11.
6. Pleyer L, et al. Molecular and cellular mechanisms of CLL: novel therapeutic approaches. Nat Rev Clin Oncol. 2009;6(7):405–18.
7. Rai KR, et al. Clinical staging of chronic lymphocytic leukemia. Blood. 1975;46(2):219–34.
8. Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981;48:198–204.
9. Cramer P, Hallek M. Prognostic factors in chronic lymphocytic leukemia—what do we need to know? Nat Rev Clin Oncol. 2011;8(1):38–47.
10. Hamblin TJ, et al. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood. 1999;94(6):1848–54.
11. Stilgenbauer S, et al. Clonal evolution in chronic lymphocytic leukemia: acquisition of high-risk genomic aberrations associated with unmuted VH, resistance to therapy, and short survival. Haematologica. 2007;92(9):1242–5.
12. Danle RN, et al. CD38 expression labels an activated subset within chronic lymphocytic leukemia clones enriched in proliferating B cells. Blood. 2007;110(9):352–9.
13. Ghia P, et al. The pattern of CD38 expression defines a distinct subset of chronic lymphocytic leukemia (CLL) patients at risk of disease progression. Blood. 2003;101(4):1262–9.
14. Orchard JA, et al. ZAP-70 expression and prognosis in chronic lymphocytic leukemia. Lancet. 2004;363(9403):105–11.
15. Rassenti LZ, et al. ZAP-70 compared with immunoglobulin heavy-chain gene mutation status as a predictor of disease progression in chronic lymphocytic leukemia. N Engl J Med. 2004;351(9):893–901.
16. Schroers R, et al. Combined analysis of ZAP-70 and CD38 expression as a predictor of disease progression in B-cell chronic lymphocytic leukemia. Leukemia. 2005;19(5):750–8.
17. Dolmer H, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343(26):1910–6.
18. Hallek M, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010;376(9747):1164–74.
19. Tsimeridou AM, et al. Chemoimmunotherapy may overcome the adverse prognostic significance of 11q deletion in previously untreated patients with chronic lymphocytic leukemia. Cancer. 2009;115(2):373–80.
20. Stilgenbauer S, et al. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphatic Leukemia Study Group. J Clin Oncol. 2009;27(24):3994–4001.
21. Zera T, et al. TP53 mutation and survival in chronic lymphocytic leukemia. J Clin Oncol. 2010;28(29):4473–9.
22. Gunnarson R, et al. Array-based genomic screening at diagnosis and during follow-up in chronic lymphocytic leukemia. Haematologica. 2011;96(8):1161–9.
23. Ouillette P, et al. Acquired genomic copy number aberrations and survival in chronic lymphocytic leukemia. Blood. 2011;118(11):3051–61.
24. Knight SJ, et al. Quantification of subclonal distributions of recurrent genomic aberrations in paired pre-treatment and relapse samples from patients with B-cell chronic lymphocytic leukemia. Leukemia. 2012.
25. Puente XS, et al. Whole-genome sequencing identifies recurrent mutations in chronic lymphocytic leukaemia. Nature. 2011;475(7354):101–5.
26. Wang L, et al. SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. N Engl J Med. 2011;365(26):2497–506.
27. Quesada V, et al. Exome sequencing identifies recurrent mutations of the splicing factor SF3B1 gene in chronic lymphocytic leukaemia. Nat Genet. 2011;44(1):47–52.
28. Fabbri G, et al. Analysis of the chronic lymphocytic leukaemia coding genome: role of NOTCH1 mutational activation. J Exp Med. 2011;208(7):1389–401.
29. Rossi D, et al. Mutations of NOTCH1 are an independent predictor of survival in chronic lymphocytic leukemia. Blood. 2012;119(2):521–9.
30. Rossi D, et al. Mutations of the SF3B1 splicing factor in chronic lymphocytic leukemia: association with progression and fludarabine-refractoriness. Blood. 2011;118(26):6904–8.
31. Group CTC Chemotherapeutic options in chronic lymphocytic leukaemia: a meta-analysis of the randomized trials. CTT Trialsists' Collaborative Group. J Natl Cancer Inst. 1999;91(10):861–8.
32. Dores GM, et al. Chronic lymphocytic leukaemia and small lymphocytic lymphoma: overview of the descriptive epidemiology. Br J Haematol. 2007;139(5):809–19.
33. Yancik R. Cancer burden in the aged: an epidemiologic and demographic overview. Cancer. 1997;80(7):1273–83.
34. Extermann M, et al. Comorbidity and functional status are independent in older cancer patients. J Clin Oncol. 1998;16(4):1582–7.
35. Bosch F, et al. Rituximab, fludarabine, cyclophosphamide, and mitoxantrone: a new, highly active chemoimmunotherapy regimen for chronic lymphocytic leukemia. J Clin Oncol. 2009;27(27):4578–84.
36. Rai KR, et al. Long-Term Survival Analysis of the North American Intergroup Study C9011 Comparing Fludarabine (F) and Chlorambucil (C) in Previously Untreated Patients with Chronic Lymphocytic Leukemia (CLL). ASH Annual Meeting Abstracts. 2009;114(22):536.
37. Varghese AM, Rawstron AC, Hillmen P. Eradicating minimal residual disease in chronic lymphocytic leukemia: should this be the goal of treatment? Curr Hematol Malig Rep. 2010;5(3):138–49.
38. Catovsky D, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial. Lancet. 2007;370(9583):230–9.
39. Rai KR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. N Engl J Med. 2000;343(24):1750–7.
40. Hallek M, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukemia: a randomised, open-label, phase 3 trial. Lancet. 2011;378(9797):1164–74.

41. Robak T, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol. 2010;28(10):1756–65.

42. Badoux XC, et al. Cyclophosphamide, fludarabine, alemtuzumab, and rituximab as salvage therapy for heavily pretreated patients with chronic lymphocytic leukemia. Blood. 2011;118(8):2085–93.

43. Osterborg A, et al. Phase II multicenter study of human CD52 antibody in previously treated chronic lymphocytic leukemia. European Study Group of CAMPATH-1H Treatment in Chronic Lymphocytic Leukaemia. J Clin Oncol. 1997;15(4):1567–74.

44. Cortelezzi A, et al. Low-dose subcutaneous alemtuzumab in refractory chronic lymphocytic leukaemia (CLL): results of a prospective, single-arm multicentre study. Leukemia. 2009;23(11):2027–33.

45. Pettitt AR, Matutes E, Oscier D. Alemtuzumab in combination with high-dose methylprednisolone is a logical, feasible and highly active therapeutic regimen in chronic lymphocytic leukaemia patients with p53 defects. Leukemia. 2006;20(8):1441–5.

46. Parikh SA, et al. Frontline chemoimmunotherapy with fludarabine, cyclophosphamide, alemtuzumab, and rituximab for high-risk chronic lymphocytic leukemia. Blood. 2011;118(8):2062–8.

47. Montillo M, et al. An open-label, pilot study of fludarabine, cyclophosphamide, and alemtuzumab in relapsed/refractory patients with B-cell chronic lymphocytic leukemia. Blood. 2011;118(15):4079–85.

48. Dreger P, et al. Allogeneic stem cell transplantation provides durable disease control in poor-risk chronic lymphocytic leukemia: long-term clinical and MRD results of the German CLL Study Group CLL3X trial. Blood. 2011;116(4):2438–47.

49. Dreger P, et al. Indications for allogeneic stem cell transplantation in chronic lymphocytic leukemia: the EBMTR transplant consensus. Leukemia. 2007;21(1):12–7.

50. Schetelig J, et al. Allogeneic hematopoietic stem-cell transplantation for chronic lymphocytic leukemia with 17p deletion: a retrospective European Group for Blood and Marrow Transplantation analysis. J Clin Oncol. 2008;26(31):5094–100.

51. Delgado J, et al. Does reduced-intensity allogeneic transplantation confer a survival advantage to patients with poor prognosis chronic lymphocytic leukaemia? A case-control retrospective analysis. Ann Oncol. 2009;20(12):2007–12.

52. Sorror ML, et al. Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. J Clin Oncol. 2008;26(30):4912–20.

53. Brion A, et al. Autologous transplantation in CLL patients with B and C Binet stages: final results of the prospective randomized GOELAMS LLC 98 trial. Bone Marrow Transplant. 2011.

54. Sutton L, et al. Autologous stem cell transplantation as a first-line treatment strategy for chronic lymphocytic leukemia: a multicenter, randomized, controlled trial from the SFMG-TC and GFLLC. Blood. 2011;117(23):6109–19.

55. Bosch F, et al. Fludarabine, cyclophosphamide, and mitoxantrone as initial therapy of chronic lymphocytic leukaemia: high response rate and disease eradication. Clin Cancer Res. 2008;14(1):155–61.

56. Moreton P, et al. Eradication of minimal residual disease in B-cell chronic lymphocytic leukemia after alemtuzumab therapy is associated with prolonged survival. J Clin Oncol. 2005;23(13):2971–9.

57. O'Brien SM, et al. Alemtuzumab as treatment for residual disease after chemotherapy in patients with chronic lymphocytic leukemia. Cancer. 2003;98(12):2657–63.

58. Schweighofer CD, et al. Consolidation with alemtuzumab improves progression-free survival in patients with chronic lymphocytic leukaemia (CLL) in first remission: long-term follow-up of a randomized phase III trial of the German CLL Study Group (GCLLSG). Br J Haematol. 2009;144(1):95–8.

59. Wierda WG, et al. Self-administered, subcutaneous alemtuzumab to treat residual disease in patients with chronic lymphocytic leukemia. Cancer. 2011;117(1):116–24.

60. Foon KA, et al. Chemoimmunotherapy with low-dose fludarabine and cyclophosphamide and high dose rituximab in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol. 2009;27(4):498–503.

61. Bosch F, et al. Rituximab Maintenance In Patients with Chronic Lymphocytic Leukemia (CLL) After Upfront Treatment with Rituximab Plus Fludarabine, Cyclophosphamide, and Mitoxantrone (R-FCM): Final Results of a Multicenter Phase II Trial On Behalf of the Spanish CLL Study Group (GELLC). ASH Annual Meeting. Abstracts. 2011;118(21):293–

62. Knauf WU, et al. George A. Follows, Donald Milligan, et al. Pocock. Rituximab Plus Chlorambucil In Patients with CD20-Positive B-Cell Chronic Lymphocytic Leukemia (CLL): Final Response Analysis of An Open-Label Phase II Study. Blood (ASH Annual Meeting Abstracts), Nov 2010;116:697.

63. Knauf WU, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol. Sep 10, 2009;27(26):4378–84. Epub Aug 3 2009.

64. Ozegowski WKD. W-[bis-(chloroethyl)-amino-benzimidazolyl-(2)]-propionic or butyric acids as potential cytostatic agents. J Prakt Chem. 1963;20(12):178–86.

65. Knauf W. Bendamustine in the treatment of chronic lymphocytic leukemia. Expert Rev Anticancer Ther. 2009;9(2):165–74.

66. Fischer K, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2011;29(26):3599–606.

67. Coiffler B, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukaemia: a phase 1–2 study. Blood. 2008;111(3):1094–100.

68. Wierda WG, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol. 2010;28(10):1749–55.

69. Wierda WG, et al. Ofatumumab is active in patients with fludarabine-refractory CLL irrespective of prior rituximab: results from the phase 2 international study. Blood. 2011;118(19):5126–9.

70. Schuh A. Anti-CD20: tales of identical twins? Blood. 2011;118(19):5066–7.

71. Jaglowski SM, et al. The clinical application of monoclonal antibodies in chronic lymphocytic leukemia. Blood. 2008;111(9):3705–14.

72. Robak T. GA-101, a third-generation, humanized and glyco-engineered anti-CD20 mAb for the treatment of B-cell lymphoid malignancies. Curr Opin Investig Drugs. 2009;10(6):588–96.

73. Bologna L, et al. Mechanism of action of type II, glycoengineered, anti-CD20 monoclonal antibody GA101 in B-chronic lymphocytic leukemia whole blood assays in comparison with rituximab and alemtuzumab. J Immunol. 2011;188(6):3762–9.

74. Patz M, et al. Comparison of the in vitro effects of the anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukaemia: a prospective, single-arm, open-label randomized phase II international study. J Clin Oncol. 2011;29(19):3599–606.

75. Morschhauser F, et al. Phase I Study of RO5072759 (GA101) in Relapsed/Refractory Chronic Lymphocytic Leukemia. ASH Annual Meeting. Abstracts. 2009;114(22):884–

76. Chanan-Khan A, et al. Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. J Clin Oncol. 2006;24(3):5343–9.

77. Ferzaghi A, et al. Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. Blood. 2008;111(11):5291–7.

78. Chen CL, et al. Single-agent lenalidomide in the treatment of previously untreated chronic lymphocytic leukemia. J Clin Oncol. 2011;29(9):1751–81.

79. Badoux XC, et al. Lenalidomide as initial therapy of elderly patients with chronic lymphocytic leukemia. Blood. 2011;118(13):3489–98.

80. Lin TS, et al. Phase II study of flavopiridol in relapsed chronic lymphocytic leukemia demonstrating high response rates in genetically high-risk disease. J Clin Oncol. 2009;27(15):6012–8.

81. Ma S, Rosen ST. Signal transduction inhibitors in chronic lymphocytic leukemia. Curr Opin Oncol. 2011;23(6):601–8.
82. O’Brien SM, et al. Phase I to II multicenter study of oblimersen sodium, a Bel-2 antisense oligonucleotide, in patients with advanced chronic lymphocytic leukemia. *J Clin Oncol*. 2005;23(30):7697–702.

83. O’Brien S, et al. Randomized phase III trial of fludarabine plus cyclophosphamide with or without oblimersen sodium (Bel-2 antisense) in patients with relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol*. 2007;25(9):1114–20.

84. O’Brien SM, et al. Phase I study of oblimersen mesylate (GX15–070), a small molecule pan-Bcl-2 family antagonist, in patients with advanced chronic lymphocytic leukemia. *Blood*. 2009;113(2):299–305.

85. Tse C, et al. ABT-263: a potent and orally bioavailable Bcl-2 family inhibitor. *Cancer Res*. 2008;68(9):3421–8.

86. Wilson WH, et al. Navitoclax, a targeted high-affinity inhibitor of BCL-2, in lymphoid malignancies: a phase 1 dose-escalation study of safety, pharmacokinetics, pharmacodynamics, and antitumour activity. *Lancet Oncol*. 2010;11(12):1149–59.

87. Kipps TJ, et al. Navitoclax (ABT-263) Plus Fludarabine/Cyclophosphamide/Rituximab (FCR) or Bendamustine/Rituximab (BR): A Phase 1 Study in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL). *ASH Annual Meeting. Abstracts*. 2011;118(21):3904–.

88. Sinisalo M, et al. Antibody response to 7-valent conjugated pneumococcal vaccine in patients with chronic lymphocytic leukaemia. *Vaccine*. 2007;26(1):82–7.

89. Hamblin AD, Hamblin TJ. The immunodeficiency of chronic lymphocytic leukaemia. *Br Med Bull*. 2008;87:49–62.

90. Dearden C. Disease-specific complications of chronic lymphocytic leukemia. *Hematology Am Soc Hematol Educ Program*. 2008;450–6.

91. Richter MN. Generalized Reticular Cell Sarcoma of Lymph Nodes/Associated with Lymphatic Leukemia. *Am J Pathol*. 1928;4(4): p. 285–292 7.

92. Rossi D, et al. Biological and clinical risk factors of chronic lymphocytic leukemia transformation to Richter syndrome. *Br J Haematol*. 2008;142(2):202–15.

93. Tsimeridou AM, Keating MJ, Wierda WG. Richter’s transformation in chronic lymphocytic leukemia. *Curr Hematol Malig Rep*. 2007;2(4):265–71.

94. Bokorny B, Codreanu I, Dasanu CA. Hodgkin lymphoma as Richter transformation in chronic lymphocytic leukaemia: a retrospective analysis of world literature. *Br J Haematol*. 2012;156(1):50–66.

95. Rossi D, et al. The genetics of Richter syndrome reveals disease heterogeneity and predicts survival after transformation. *Blood*. 117(12):3391–401.

96. Tsimeridou AM, et al. Clinical outcomes and prognostic factors in patients with Richter’s syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation. *J Clin Oncol*. 2006;24(15):2343–51.

97. Bokorny B, Codreanu I, Dasanu CA. Hodgkin lymphoma as Richter transformation in chronic lymphocytic leukaemia: a retrospective analysis of world literature. *Br J Haematol*. 156(1):50–66.

98. Tsimeridou AM, et al. Fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone plus rituximab and granulocyte-macrophage-colony stimulating factor (GM-CSF) alternating with methotrexate and cytarabine plus rituximab and GM-CSF in patients with Richter syndrome or fludarabine-refractory chronic lymphocytic leukemia. *Cancer*. 2003;97(7):1711–20.

99. Tsimberidou AM, et al. Phase II study of fludarabine, cytarabine (Ara-C), cyclophosphamide, cisplatin and GM-CSF (FACPGM) in patients with Richter’s syndrome or fludarabine-refractory chronic lymphocytic leukemia. *Blood*. 2007;113(2):299–305.

100. Rodriguez J, et al. Allogeneic haematopoietic transplantation for Richter’s syndrome or fludarabine-refractory chronic lymphocytic leukemia. *J Clin Oncol*. 2008;26(2):196–203.

101. Rodriguez J, et al. Allogeneic haematopoietic transplantation for Richter’s syndrome. *Br J Haematol*. 2000;110(4):897–9.

---

**Publish with Libertas Academica and every scientist working in your field can read your article**

“I would like to say that this is the most author-friendly editing process I have experienced in over 150 publications. Thank you most sincerely.”

“The communication between your staff and me has been terrific. Whenever progress is made with the manuscript, I receive notice. Quite honestly, I’ve never had such complete communication with a journal.”

“LA is different, and hopefully represents a kind of scientific publication machinery that removes the hurdles from free flow of scientific thought.”

**Your paper will be:**
- Available to your entire community free of charge
- Fairly and quickly peer reviewed
- Yours! You retain copyright

**http://www.la-press.com**

---

178 Clinical Medicine Insights: Oncology 2012:6