Research Review Speaker Series™

Advances in the treatment of chronic lymphocytic leukaemia

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About the Speaker

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John Gribben is the Hamilton Fairley Professor of Medical Oncology at Barts and The London School of Medicine, Queen Mary University of London. After doctoral studies at University College London where he was the recipient of a Wellcome Trust Fellowship award, he received a Fogarty International Fellowship from MRC in 1989 to continue post-doctoral training at the Dana-Farber Cancer Institute, Harvard Medical School. In 1992, he was appointed to the Faculty at Harvard Medical School, where he remained as Associate Professor of Medicine and an Attending Physician at the Dana-Farber Cancer Institute and Brigham and Women's Hospital, until returning to London in 2005. He is an internationally recognised translational cancer researcher and the author of more than 400 manuscripts and book chapters. His primary research interests include the management of lymphoma, leukaemia and CLL, immunotherapy of cancer, including stem-cell transplantation, the characterisation of tumor antigens, and eradication of minimal residual disease. He is the Chair of the international workshop for NHL (iwNHL), a member of the American Society for Clinical Investigation and in 2008 was elected a Fellow of the Academy of Medical Science. He was an Editor of Blood from 2007–2014 and has recently been appointed to the Board of the European Hematology Association.

Disclosures

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This publication is a summary of a recent presentation in New Zealand by Professor John Gribben, Chair of Medical Oncology at the Barts Cancer Institute, Queen Mary University of London, UK. The landscape for chronic lymphocytic leukaemia (CLL) treatment options in the USA and Europe has changed, with a number of novel agents for CLL recently receiving FDA and EMA approval. Professor Gribben discussed how these new agents are being applied and highlighted the ways in which these treatments will potentially enhance the management of patients with CLL.

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Remarkable progress has been made over a short period of time. The first study to demonstrate any improvement in response rates, remission and progression-free survival with an alternative agent to chlorambucil was presented as recently as 2000, in support of fludarabine as an initial treatment for CLL.[1] Since then, treatment has progressed from single-agent regimens with purine analogues and combinations that increased the remission rate, although there was no evidence to suggest an overall improvement in survival.[2] Until recently, the prevailing belief was that perhaps you could start treating a CLL patient more gently; at relapse, consider the next treatment; and escalate therapy thereafter. This approach has changed with the advent of a number of new therapeutic agents. The introduction of chemoimmunotherapy resulted in a survival advantage in CLL when treated with fludarabine-containing front-line regimens that include cyclophosphamide and rituximab (FCR) over FC alone.[3] This evidence has led to the conviction that the best regimen should always be used first.

Within the last year, the UK has witnessed the approval of next-generation anti-CD20 agents (in combination with chlorambucil) for previously untreated CLL, as well as approval for B-cell receptor (BCR) signalling inhibitors for treatment of relapsed/refractory disease and previously untreated CLL with 17p deletion (del(17p))/*TP53* mutations. The availability of these new agents impacts the way in which clinicians approach CLL; *TP53* defects are often resistant to standard chemoimmunotherapy and are associated with considerably shorter overall survival (OS) in CLL patients as compared with those without *TP53* defects (~3 years).[3] Access to molecular analysis is desirable, as it enables clinicians to examine mutations and deletions before initiation of treatment and facilitate optimal outcomes for individual patients. These new agents greatly increase the options that clinicians have for treating their patients and tailoring treatment to their individual needs, based on the specifics of the person's disease and comorbidities.

Issues that Prof. Gribben considers when treating CLL

Does the patient require treatment or can we continue to watch and wait until they are sufficiently symptomatic from their disease? If treatment is needed:

1. What is the goal of therapy? (Discussions need to be held with the patient and family, to consider whether to use more aggressive therapies with potential benefit but also higher toxicities as compared with milder therapy that has less benefit).
2. What comorbidities are present to determine "fitness" for specific chemoimmunotherapy? (Is the patient fit for full-dose FCR? If not, other options can be discussed).
3. Is there a del(17p)/*TP53* mutation that would make chemotherapy a less attractive option? (Patients with such anomalies would be offered novel therapeutic agents).

The current UK treatment algorithm in CLL is as follows:

Current UK treatment algorithm in CLL

Stage	Fitness	del(17p) *p53*mut	Therapy
Binet A-B, Rai 0-II, inactive	Irrelevant	Irrelevant	Watch and wait
Active disease or Binet C or Rai III-IV	Go go	No	FCR, BR
		Yes	Allo-SCT BCR signalling inhibitor
	Slow go	No	Obinutuzumab + Clb
		Yes	BCR signalling inhibitor

FCR = fludarabine/cyclophosphamide/rituximab; BR = bendamustine/rituximab; Allo-SCT = allogeneic haematopoietic stem cell transplantation; Clb = chlorambucil; BCR = B-cell receptor.

In the presence of del(17p)/*TP53* mutation, the UK algorithm suggests the use of BCR signalling inhibitor over allogeneic haematopoietic stem cell transplantation, which has been moved into second position by the current US and European guidelines upon the availability of these novel agents. Prof. Gribben noted that, at his centre, very few allo-SCTs for CLL have been needed in the past 2 years, due to the use of novel agents. Notably, fitness becomes less of an issue with the novel agents, because older- and younger-age patients are able to tolerate these agents equally well.

Management of fit CLL patients

The German CLL Study Group (GCLLSG) CLL8 trial was the first randomised trial to demonstrate an overall survival advantage with any treatment, in this case with chemoimmunotherapy, compared to chemotherapy.[3,4] Over a median 5.9 years of observation time, 69.4% of patients in the FCR arm remained alive (median OS not reached) versus 62.3% in the FC arm (median 86 months) (HR 0.68; 95% CI, 0.535 to 0.858; p=0.001). As the OS data mature, the survival curves are continuing to separate even further. These data support frontline FCR as the treatment of choice for CLL patients whenever possible, as this will confer a survival advantage.

This survival plateau effect is echoed in long-term follow-up data for FCR from the MD Anderson Cancer Center, in which sequencing of immunoglobulin heavy chains (*IgHV*) mutation status stratified CLL into clinically relevant prognostic subgroups – mutated *IgHV* and unmutated *IgHV*.[5] These data show that mutated *IgHV* is associated with better survival (PFS and OS) and clinical course, with an apparent PFS plateau at ~60% on the FCR curve. Up to now, CLL has been considered incurable except with an allogeneic stem cell transplant. These data indicate that potentially, about 60% of CLL patients with mutated immunoglobulin genes can be cured with FCR. In contrast, patients with unmutated *IgHV* continue to have worse outcomes, with a continuing fall in the survival curve. It is suggested that this patient population needs a different type of therapy – either with the addition of other therapies or a maintenance approach that would move the survival curve upwards. These findings are supported by similar findings from the German CLL Study Group.

The GCLLSG CLL8 trial has also shown that minimal residual disease (MRD) levels after chemoimmunotherapy independently predict PFS and OS in CLL, with a high, intermediate and low risk of disease progression seen in patients with >1%, 0.01–1%, or <0.01% MRD respectively.[6] Notably, FCR induced low MRD levels more frequently than FC. These data suggest that the goal of therapy is to maintain patients in a MRD-negative state. This idea is reinforced by an evaluation of PFS/OS according to peripheral blood (PB) and bone marrow (BM) MRD levels in the ADMIRE/ARCTIC trials, which showed that achieving MRD negativity (<0.01%) with FCR-type therapy was associated with an extremely good outcome.[7]

The CLL8 trial selected only patients with a good physical fitness (Cumulative Index Rating Scale [CIRS] score of ≤6). Even in this fit population, comorbidities influenced outcome; the risk of mortality was doubled for patients with a CIRS score >3 compared with those who had a CIRS score of 0–3.[8] Patients with worse outcomes had more comorbidities, who were unable to tolerate full FCR doses and all scheduled cycles. Subsequently, the GCLLSG initiated the CLL10 trial in order to test the non-inferiority regarding efficacy and potentially better tolerability of bendamustine plus rituximab (BR) compared with FCR in first-line therapy of physically fit CLL patients (CIRS score ≤6) without del(17p).[9] The trial failed to meet the primary endpoint: PFS was significantly prolonged with FCR compared with BR (median 55.2 months vs 41.7 months; p<0.001). However, in this study, there was an unplanned lack of balance between the two arms as to the mutational status of immunoglobulin genes, with more unmutated cases in the BR arm than in the FCR arm. Secondly, the between-group difference in PFS disappeared in fit patients aged >65 years; in this age group, not all patients could tolerate full-dose FCR. Worldwide, these study data have been interpreted as indicating that BR is good but inferior to FCR in patients able to tolerate both, whereas German investigators have interpreted the data to mean that patients aged >65 years should be offered BR rather than FCR.

Management of unfit CLL patients

CLL is a disease of the elderly. The median age at diagnosis is 72 years among Western populations[10-13] (younger in Asian populations); ~70% of CLL patients are aged ≥65 years at time of diagnosis,[10] 40% of patients are aged >75 years[11] and the prevalence is likely to increase due to the ageing population.[12] Nevertheless, decisions on the treatment of CLL are being made on the basis of clinical trials that have enrolled patients who are younger and fitter than the majority of CLL patients seen in practice. Thus, evidence from clinical trials has not reflected real-world outcomes. Fitness and comorbidity burden are an important consideration in the selection of appropriate therapy: 89% of CLL patients have one or more comorbidity and 46% of patients have at least one major comorbidity.[14] Effective treatment options have been limited for:

- Patients with high-risk genetic alterations
- Patients who relapse early after first-line therapy
- Patients who have received multiple prior therapies
- Frail or elderly patients with front-line or relapsed disease

The CIRS score was developed as a method of quantifying comorbidity burden.[15,16] Many CLL trials are using the CIRS score, which may be modified (whereby CLL disease is awarded 3 or 4 points in the cumulative score), or disease-adjusted; it is important to determine what system has been used in a particular clinical trial population. For many years, the CIRS score has been used in patients with solid tumours. A CIRS score of 6 differentiates between patients who are eligible for intensive chemotherapy and those who are not (fit versus unfit patients).[17]

The CLL11 trial of obinutuzumab was the first study that assessed the benefits of chemoimmunotherapy in patients aged ≥18 years with previously untreated CLL and coexisting conditions (i.e. first-line FCR-ineligible CLL).[18] 781 patients with a CIRS score >6 and/or estimated creatinine clearance (CrCl) 30–69 mL/min were randomised to receive obinutuzumab plus chlorambucil (G-Clb), rituximab plus chlorambucil (R-Clb), or Clb alone. Caveats to this study include the GCLLSG approach to chlorambucil dosing (0.5 mg/kg day 1 and day 15 cycles 1–6, every 28 days, whereas the UK practice is to use a higher chlorambucil exposure). Also, the rituximab dose was a standard CLL dose (375 mg/m^2 day 1 cycle 1, 500 mg/m^2 day 1 cycles 2–6, every 28 days), while obinutuzumab was dosed as 1,000 mg on days 1/2, 8 and 15 of cycle 1, then on day 1 of cycles 2–6, every 28 days. This difference in dosing has been questioned, but extensive pharmacodynamic/pharmacokinetic analysis has established that the obinutuzumab dosing schedule used in CLL11 is the optimal dose and frequency, based upon levels of the drug when administered in this way.

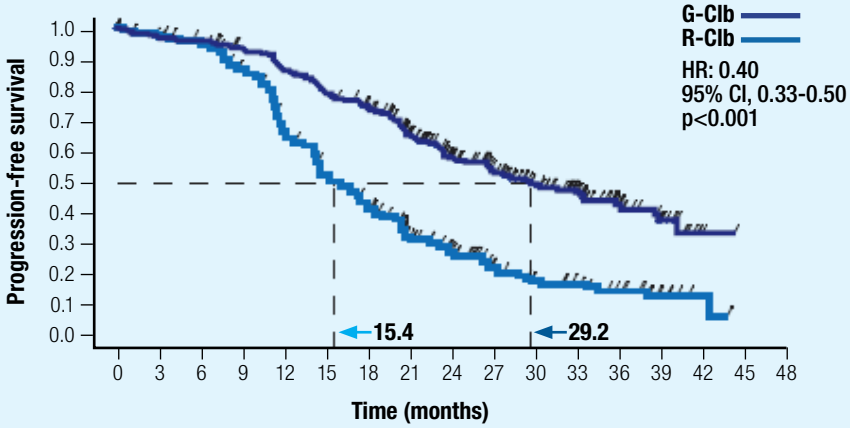
The CLL study found that G-Clb improved response rates and prolonged survival compared with R-Clb or Clb alone. Significant increases in overall response rates were seen with G-Clb versus R-Clb (78.4% vs 65.1%) and versus Clb alone (77.3% vs 31.4%). Complete responses (CRs) were found in 21% versus 7% of patients with G-Clb versus R-Clb, and in no patients on Clb alone. Moreover, the addition of obinutuzumab to chlorambucil led to MRD-negativity in peripheral blood in 38% of patients and in bone marrow in 20%, versus just 3% and 3%, respectively, of patients in the R-Clb arm and none of the patients on Clb monotherapy.

The most recently published data from the CLL11 study demonstrate a significant improvement in PFS for patients treated with G-Clb over Clb alone (HR 0.18; 95% CI, 0.14 to 0.24; p<0.0001) and also a marked superiority with the obinutuzumab combination over R-Clb (HR 0.40; 95% CI, 0.33 to 0.50; p<0.001).[19] The CLL11 study allowed patients with progressive disease in the chlorambucil arm to cross over to G-Clb. Despite that, the OS data demonstrate a survival advantage for starting G-Clb versus starting with Clb alone; at a median follow-up of 34.8 months, the HR was 0.47 (95% CI, 0.29 to 0.76; p=0.0014). Prof. Gribben noted that these data support the contention that it is inappropriate to start patients with CLL on Clb monotherapy; CLL patients should be offered optimal therapy from the beginning. The OS data for the comparison between G-Clb and R-Clb are still immature; many more patients in the obinutuzumab-containing arm remain in remission and their survival curve continues to separate out from the R-Clb arm (see Fig. 1).

CLL11 study data on PFS by MRD status in patients treated with G-Clb demonstrate the importance of achieving MRD-negativity, as this is associated with a vastly improved outcome compared with being MRD-positive.[18] Prof. Gribben noted that this reinforces the notion that even in the less-fit, older patients, treatment should drive towards a deep remission to give these patients a long progression-free interval and long periods where they will be able to avoid returning to hospital for more treatments and reduce the likelihood of complications from their underlying disease.

The CLL11 study demonstrated a higher frequency of infusion-related reactions (IRRs), particularly occurring on day 1 of cycle 1, of G-Clb as compared with R-Clb (all grades 66% vs 38%, respectively). Prof. Gribben considers that obinutuzumab-associated IRRs in the clinical setting will not be quite as high as the rates observed in CLL11, because of what has been learned subsequently about how to mitigate against them. Prof. Gribben explained that considerable clinical trial and clinical practice experience in the UK has revealed that the IRRs associated with obinutuzumab are most likely to occur on cycle 1 day 1 (IRRs with subsequent infusions are rare) and are generally clinically manageable. Carefully managing these IRRs avoids unnecessary discontinuation of treatment and suboptimal outcomes for patients. Prof. Gribben noted that adequate premedication is important (see text box on p.4 detailing UK clinical practice) and that staff need to be vigilant for potential IRRs and take prompt action. Patients should also be informed about the types of symptoms they might expect. Compared to IRRs with rituximab, he has noticed that the IRRs typically occur earlier in the first infusion (within the first 2 hours), but that these only occur in the first cycle, so there is confidence that patients who have reactions with the first infusion are unlikely to react to subsequent infusions so that further treatment should not be curtailed.

Figure 1. Updated CLL11 progression-free survival data: obinutuzumab-chlorambucil vs rituximab-chlorambucil.[19]



No. at risk

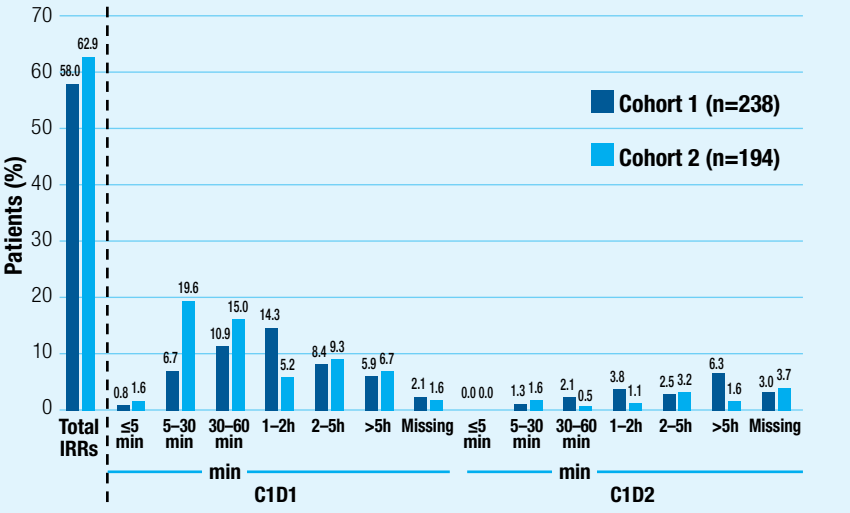
G-Clb:	333	307	302	288	267	243	221	172	124	99	75	45	25	12	1	0
R-Clb:	330	317	309	273	204	160	128	82	59	38	26	20	13	4	1	0

G-Clb = obinutuzumab-chlorambucil; R-Clb = rituximab-chlorambucil.

In CLL11, grade ≥3 IRRs and neutropenia were more common with G-Clb than with R-Clb (fewest with Clb monotherapy), but the risk of infection was not increased.[18]

The ongoing phase IIIb GREEN study of obinutuzumab alone or in combination with chemotherapy sought to reduce IRRs on the first day of obinutuzumab administration in 783 fit and unfit patients aged ≥18 years with previously untreated CLL (cohort 1) or relapsed/refractory CLL (cohort 2).[20] Treatment consisted of 6 cycles of obinutuzumab alone or in combination with 28-day cycles of chemotherapy of physician choice: FC for fit patients (CIRS ≤6 and CrCl ≥70 mL/min), chlorambucil for unfit patients (CIRS >6 and/or CrCl <70 mL/min) or bendamustine for fit/unfit patients. GREEN is assessing the impact of a lower (25 mg) and slower (12.5 mg/h) dose on cycle 1 day 1, as well as an additional dose of dexamethasone 12 hours prior to the infusion. Preliminary safety data show that these measures reduced the severity of the IRRs, and that most reactions occurred within the first 2 hours of the first infusion (see Fig. 2).

Figure 2. GREEN study: all-grade IRRs during cycle 1 day 1 and cycle 1 day 2 (cohorts 1 and 2).[20]



NB values at the limit of time range are included within the lower range e.g. 1–2 h means >1 h, ≤2 h

Obinutuzumab IRR mitigation strategies

In UK clinical practice, oncology nurses are using a split-dosing schedule for the first obinutuzumab dose: 100 mg on day 1 and 900 mg on day 2. Premedication for obinutuzumab consists of intravenous (IV) dexamethasone 20 mg at 1 hour prior to obinutuzumab infusion, plus IV chlorphenamine 10 mg and oral paracetamol 1000 mg at least 30 minutes before infusion starts. Patients are asked to withhold any antihypertensive medications for 24 or 48 hours before the first infusion. The nurses are asked to watch the patients very carefully at the start of the infusion and proactively manage them with extra fluids.

Obinutuzumab is much more effective than rituximab at reducing white blood cell counts after the first infusion, therefore, Prof. Gribben and colleagues rarely observe IRRs with obinutuzumab after day 1 cycle 1. With careful IRR management, most patients are able to go on to receive the full course of therapy.

First-line treatment regimens for CLL

Fit patient:

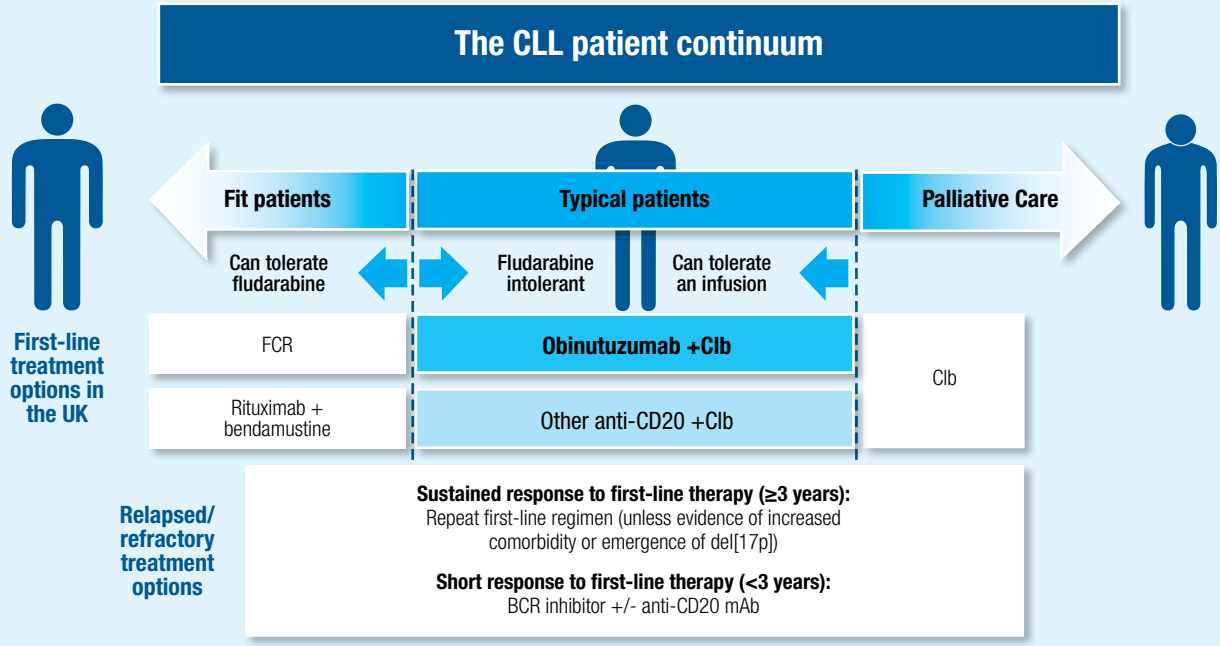
- completely independent
- no comorbidities
- normal life expectancy
- aggressive immunochemotherapy

FCR is the treatment of choice. Rixtuximab plus bendamustine might be of value in the presence of any contraindications to a purine analogue.

Typical CLL patient:

- some comorbidities
- impaired organ function
- reduced performance status
- less aggressive approach

Obinutuzumab plus chlorambucil is the first-line option. The patient may potentially be a candidate for rituximab-chlorambucil.



Classifying fitness is important

There is a need to accurately categorise life expectancy unrelated to CLL. Physicians have to inform patients through counselling and define the importance of durable disease control. Physicians often underestimate life expectancy. If the life expectancy in the overall population is around 78 years, and a 75-year-old patient presents with CLL, is it reasonable to expect that this patient has a life expectancy of another 3 years? However, such a person has already survived all those illnesses that kill people before the age of 75 years: US (and European) data show that 75-year-olds can expect to live for an average 11.9 years for men and 13.6 years for women.[21] CLL has a major impact upon survival in patients aged <55 years compared with the age-matched general population; the same is true for patients aged 55–64 years and 65–74 years at diagnosis, but not those aged ≥75 years.[22] In these elderly patients, CLL impacts not only survival, but also quality of life, infections, and admissions to hospital for other complications of the disease. Prof. Gribben believes that the ≥75-year age group has been underserved, both by physicians' perceptions and misperceptions of what the life expectancies should be for these people, as well as the lack of the right treatment tools. This is now changing.

Real-life patient populations have historically differed considerably from patients treated in clinical trials. Whereas the median age of 'real-world' CLL patients at presentation is 72.5 years,[23] the median age of patients was 61 years in CLL8[3] and 62.5 years in REACH.[24] However, the CLL11 trial of obinutuzumab, where the median age was 73 years, represents the real-world experience in dealing with this disease.

Comorbidity is the limiting factor in the choice of chemoimmunotherapy in CLL.[10] Determining the goals of treatment for older patients with CLL,[25] whether these concern MRD-negative remission, a good balance of treatment efficacy/toxicity, or palliation, depends upon the patients' life expectancy unrelated to CLL, reduced organ function, comorbidity and performance status, as well as honest discussion with the patient and family about their wishes as to where they sit on the spectrum of 'do no harm' versus more aggressive therapies. CIRS score can be used as a tool to assess suitability for treatment approaches.[10,26,27]

Treatment options for frail CLL patients

- FCR if the patient is deemed fit – with comorbidity and not age being the determinant factor
- FCR lite
- BR – an attractive option. However, most data are from studies in patients deemed appropriate for FCR, e.g. CLL10
- Obinutuzumab plus chlorambucil
- How do we make the correct choice?

When used as a monotherapy, bendamustine is associated with significantly prolonged PFS as compared with chlorambucil (median 21.6 months vs 8.3 months; p<0.0001) in first-line CLL patients.[28] The CLL10 study of FCR versus BR in fit first-line patients found a median PFS of 55.2 months versus 41.7 months, respectively.

At iwCLL2015, data from the MaBLe study were presented, comparing the efficacy and safety of BR with R-Clb in fludarabine-ineligible patients with CLL.[29] At a median follow-up of 24 months, CR rates with BR were significantly increased compared to R-Clb (confirmed CR rates: 24% vs 9%; p=0.002). The median PFS was 39.6 months with BR versus 29.9 months with R-Clb. Prof. Gribben noted that this PFS with R-Clb was much longer than has been seen in other studies (e.g. 15.7 months in CLL11) and postulates that this may be due to a very different patient population from that enrolled in CLL11. The available MaBLe data do not describe the patient characteristics and more information is required before the place for this regimen can be determined.

Novel agents in CLL

New insights into pathogenesis have created many promising diagnostic and therapeutic options. Treatment-refractory CLL represents a great unmet medical need. Data from the MD Anderson Cancer Center reveal that once a patient has failed fludarabine, the median survival is 11 months; CLL is no longer an indolent, slow-growing disease (Keating MJ, MDACC – personal communication with Prof. Gribben). Evidence shows that CLL with *TP53* mutation is as important to consider for prognostic impact as (del)17p in CLL.[30] Survival in patients with a *TP53* mutation without (del)17p overlaps that of patients with (del)17p.

Study data support the importance of mutational analysis. An analysis of data provided by Stephan Stilgenbauer from the Central Reference Laboratory for Genetics has revealed an increasing frequency of *TP53* pathways with advancing lines of therapy in CLL:

- Among untreated Binet A CLL patients in the CLL1 'watch and wait' study, ~3% had (del)17p and 5% had a *TP53* mutation (i.e. (del)17p/*TP53*mut rate: ~8%)
- In the CLL4 and CLL8 first-line treatment trials, the (del)17p rate was ~5–10%, while the *TP53* mutation rate was 6% (i.e. (del)17p/*TP53*mut rate: ~10%)
- In the CLL2H trial, involving fludarabine-refractory patients, over two-thirds of patients had (del)17p (31%) or a *TP53* mutation (35%) and therefore lack the ability to respond appropriately to chemotherapy

For relapsed/refractory CLL, alternative therapeutic agents that target the B cell receptor signalling pathway become important. Clinical trial data provide good support for the role of such treatment, which is associated with significant improvements in PFS, response rate, and OS among patients with relapsed/refractory CLL.[31,32] Indeed, in the setting of (del)17p, these novel therapeutic agents are revolutionising PFS and OS outcomes for these patients, who have previously shown only very poor survival.[33]

Salvage therapy for CLL in the UK

In the UK, standard-of-care treatment schedules for patients who are treatment-refractory or progress within 2 years of first-line chemoimmunotherapy consists of a BCR signalling inhibitor, regardless of fitness. Clinical trials are currently underway, employing novel BCR antagonists and other agents/combinations. For patients who progress after 2 years, the standard approach for all patients is to repeat/modify first-line therapy. Those who received FCR upfront are offered bendamustine-rituximab as salvage. Patients with (del)17p/*TP53* mutations, even if they relapse, are offered a BCR signalling inhibitor. Trials are also underway involving this patient population, examining the clinical efficacy of the new BCR antagonists and other agents/combinations.

In Summary

- A number of new agents have been approved in the UK recently for CLL treatment
- There is a perfect opportunity to tailor the treatment approach to the needs of the individual patient based upon their fitness and on the presence of resistance/mutations
- Specific side effect profiles with different agents have to be considered
- In the EU and USA, a new approach to management is already here

The New Zealand Perspective – Dr Robert Weinkove, Consultant Haematologist, Wellington Hospital

While cutting-edge CLL treatment is changing rapidly, funded options available in New Zealand remain limited. Nonetheless, Professor Gribben's talk raises important practice points.

Long-term follow-up of the CLL8 trial and MD Anderson series suggest that FCR is curative for nearly 60% of CLL patients with a mutated *IgHV* gene, with plateaus in progression-free survival curves after year 8. Although we do not test for it, *IgHV* is mutated in 45% of CLL cases, suggesting FCR can cure a quarter of unselected patients. This highlights the need to give the full six cycles of first-line FCR to our fitter CLL patients, if possible: the longer we can keep these patients in remission, the greater the likelihood that novel agents will be funded at the time of relapse.

For frailer patients, the latest CLL11 update demonstrates overall survival benefits for obinutuzumab and rituximab in combination with chlorambucil. Until obinutuzumab is funded, we are faced with a stark choice between FCR or chlorambucil alone. A number of NZ centres are running the CLL14 trial, which brings access to obinutuzumab. NZ cancer centres are starting to become more familiar with the use of this drug, particularly the prevention and management of infusion reactions.

The priority for patients with del(17p) or with early relapse after chemotherapy should be to access a novel agent such as a B-cell receptor (BCR) signalling inhibitor or Bcl-2 inhibitor. Professor Gribben commented that in the UK, where BCR signalling inhibitors are funded, he now rarely does transplants for CLL. Until novel agents are funded in NZ, allograft is likely to remain a feature of CLL management for fitter high-risk patients.

ABOUT RESEARCH REVIEW

Research Review is an independent medical publishing organisation producing electronic publications in a wide variety of specialist areas. Research Review publications are intended for New Zealand medical professionals.

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