THE FUTURE OF CHRONIC LYMPHOCYTIC LEUKAEMIA TREATMENT: BALANCING EFFICACY, SAFETY AND COST

A Review of the Mundipharma International Ltd Organised Symposium, at the International Workshop on Chronic Lymphocytic Leukemia (iwCLL), Cologne, Germany, 9th-11th September 2013

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Expanding Treatment Options for Less Fit CLL Patients

Dr Valentin Goede

So far, there is no objective and broadly accepted definition of the less fit chronic lymphocytic leukaemia (CLL) patient. There is great heterogeneity in fitness among elderly patients. This means that patient populations should be checked in clinical trials that claim to provide data for less fit CLL patients.

One treatment option for less fit CLL patients is chemotherapy alone; the question is which chemotherapy is the best treatment choice. There are several Phase II trials evaluating the efficacy and toxicity of fludarabine-based chemotherapy in older or unfit patients,[1-4] the results of the trials varied, the patient numbers were rather low and patient populations were heterogeneous. Therefore, it is not possible to conclude from these trials whether fludarabine treatment is more or less suitable in less fit CLL patients. The German CLL study group (GCLLSG) initiated a Phase III trial with fludarabine monotherapy[5] in elderly patients. The results showed that there was no difference in progression-free survival (PFS) between fludarabine and chlorambucil (19 months versus 18 months respectively, p=0.7). Furthermore, fludarabine did not increase overall survival (OS) (46 months in the fludarabine versus 64 months in the chlorambucil arm, p=0.15).

During recent years chemoimmunotherapy has been very successfully developed in younger, fit patients, the question is whether it can be used in unfit patients. There are ongoing Phase II trials with low-dose fludarbine-based chemoimmunotherapy (fludarabine plus cyclophosphamide plus rituximab [FCR]) in elderly and possibly less fit CLL patients.[6-8] The studies include a larger patient population and the initial data are promising, but there are no Phase III data available comparing FCR low dose regimen with any other treatments in this particular patient population.

Bendamustine is another chemotherapy option for the treatment of CLL but there are no Phase II trials specifically conducted for elderly and less fit CLL patients. However, there are promising retrospective data available[9] that show first-line treatment with bendamustine in patients with a median age of 72 years (n=10); the overall remission rate (ORR) was 10%, the complete response rate (CR) 10% and median PFS was 26 months. A larger Phase III trial[10] compared first-line bendamustine monotherapy with chlorambucil

monotherapy. The results showed that there was no OS advantage with bendamustine compared to chlorambucil, but there was a clear advantage regarding PFS (median PFS was 21.6 months with bendamustine and 8.3 months with chlorambucil, p<0.0001). Unfortunately, the median age of the patient population was 65 years which makes it difficult to draw definitive conclusions across all patient populations.

Bendamustine-based chemoimmunotherapy (bendamustine plus rituximab [BR])[11-13] is a further treatment option. Data produced by the GCLLSG[11-13] show encouraging results, particularly in one trial[11] that showed first-line treatment with BR had a promising efficacy profile and PFS of 34 months, although the median age was only 64 years. Retrospective data of BR in elderly patients[9] (median age 73 years; n=6) show encouraging response rates in first-line treatment. The overall response (OR) was 67%, CR 33% and partial response (PR) 33%. There are no Phase III data available at present for BR treatment in less fit patients. However, there is one study that is in progress,[14] the MaBLe study, which is comparing bendamustine plus rituximab with chlorambucil plus rituximab. The median age of the trial population was 75 years in the bendamustine plus rituximab arm (n=58) and 73 years in the chlorambucil plus rituximab arm (n=73). There were no data available regarding the fitness of patients but many of the patients had concomitant medications indicating the likelihood of comorbidities. The preliminary results of the study show that there was no significant difference in OR between the two treatment arms. However, there was an increased CR rate in the bendamustine plus rituximab arm. The preliminary data showed that the toxicities for both treatments were similar, suggesting that bendamustine plus rituximab was not significantly more toxic than chlorambucil plus rituximab.

Chlorambucil-based chemoimmunotherapy (chlorambucil plus rituximab [CLB-R]) is another treatment option in less fit CLL patients. Phase II trials with CLB-R in elderly patients[15,16] show promising response rates which are higher than would be expected with chlorambucil monotherapy and in one study the median PFS was 24 months.[15] A Phase III study[17] compared chlorambucil plus rituximab with chlorambucil monotherapy. The response rates and PFS were higher in patients treated with CLB-R than with chlorambucil monotherapy, this was particularly seen in unfit patients.

There are novel CLL drugs likely to be available in the near future which will further complicate treatment choice. These include lenalidomide which was pioneered in a Phase II trial in elderly patients and has been compared with chlorambucil in a Phase III trial, unfortunately the Phase III study has been stopped because of a high mortality rate in the experimental arm. ABT199 is also being studied but not specifically in unfit CLL patients. In addition, two novel CD20 antibodies (obinutuzumab and ofatumumab) are being developed. The CLL11 trial[18] is comparing GA101 plus chlorambucil (G-CLB) with chlorambucil (CLB) alone in CLL patients who are unfit and have comorbidities. The trial is showing promising response rates.[17]

Preliminary results for the OR and CR for G-CLB were better compared with the CLB arm. The median PFS showed superior efficacy with G-CLB compared to CLB alone. There are both monotherapy and combination data available on tyrosine-kinase inhibitors (TKIs), specifically in the first-line treatment of elderly patients. Ibrutinib monotherapy has been evaluated in 31 patients with a median age of approximately 70 years; preliminary results show an excellent PFS. Similarly, in elderly patients receiving a combination of idelalisib plus rituximab the PFS was very promising.[19,20]

Treatment is moving in the direction of considering the less fit patients rather than a homogenous population. It is possible that there are patients who are not completely fit but are fit enough to be treated with chemoimmunotherapy. Regimens used outside clinical trials indicate that there are a proportion of less fit patients that are good candidates for treatment with either BR or CLB-R chemoimmunotherapy. There are patients that are almost too frail to treat; for these patients there appears to be a niche for monochemotherapy, and bendamustine may be a treatment option. Rituximab and ofatumumab monotherapy are used in the USA for the treatment of this group of patients. However, there is sparse trial evidence available to support their use. The novel treatments have the potential to be used in less fit patients. The patients that would normally be treated outside of clinical trials with chemoimmunotherapy are good candidates

to be treated with chemoimmunotherapy with one of the new CD20 antibodies. Chemoimmunotherapy-free treatment can also be considered by combining novel CD20 antibodies or rituximab with a TKI. Patients who are almost frail and would usually be treated chlorambucil or bendamustine monotherapy are good candidates to be investigated for treatment with the novel drugs as a monotherapy, e.g. TKIs or possibly CD20 antibodies. This would provide additional data on the use of the novel agents and their use in less fit patients.

'Go-Go' (Patients in Good Physical Condition) CLL Patients: A Look Towards the Future

Prof Clemens Wendtner

Between 2005 and 2006 the gold standard was set by the MD Anderson Cancer Center with the fludarabine plus cyclophosphamide plus rituximab (FCR) regimen for the treatment of CLL. In addition, the GCLLSG has conducted a Phase III trial comparing fludarabine plus cyclophosphamide (FC), the old standard of care, versus FCR.[21] The results show that FCR produces a remarkable median PFS of almost 5 years and a benefit in OS in first-line CLL treatment.

FCR is the gold standard first-line treatment for go-go patients. Following a median observation time of 5.9 years the data have been updated[22] (Figure 1) and show that there is a clear difference in PFS between FCR and FC treatment. Median PFS for FCR is 57 months compared with 33 months for FC (HR 0.59; 95% CI 0.5-0.7; p<0.0001).

In addition, OS showed increased benefit for the FCR treated patients (69.4% alive, median not reached) compared with the FC treated patients (62.3% alive, median 86 months. HR 0.68; 95% CI 0.535-0.858; p=0.001); these results show that FCR is a proven standard of care for CLL patients. Böttcher et al.[23] showed that PFS and OS can be predicted by collecting peripheral blood at different time points (interim staging and first restaging) after treatment with FCR. PFS showed that irrespective of treatment the probability of negative minimum residual disease was higher using FCR than FC. This was also shown in OS.

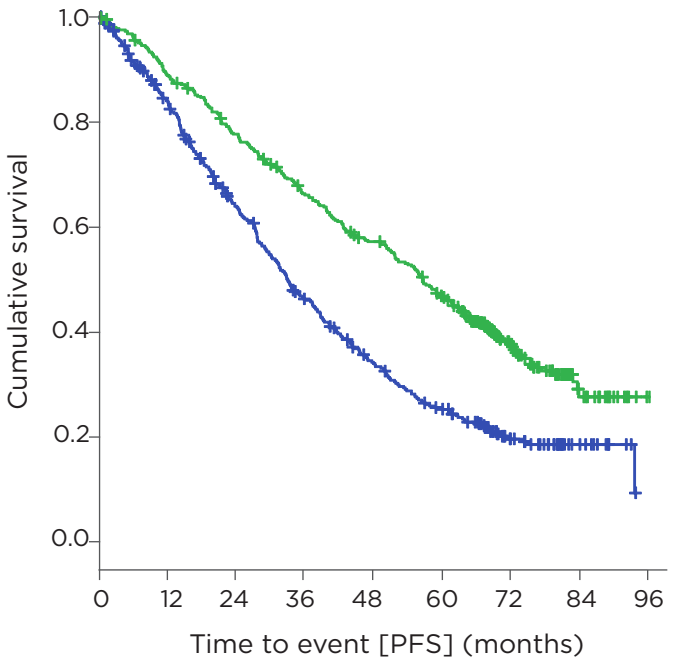

Figure 1. Addition of rituximab to fludarabine and cyclophosphamide: progression-free survival 2012. FCR: fludarabine plus cyclophosphamide plus rituximab; FC: fludarabine plus cyclophosphamide. Median observation time: 5.9 years. Median progression-free survival: FCR: 57 months, FC: 33 months. HR 0.59, 95% CI 0.5-0.7, p<0.0001. *Fischer K et al.*[22]

In go-go patients, good results have been achieved in PFS and OS using FCR but there are a fraction of patients that do not benefit in the long-term. One notion is that additional treatment is required following induction therapy in the maintenance period, e.g. lenalidomide. Consequently the CLLM1 study was established.[24] This is a Phase III, multicentre, randomised, double-blind, placebo-controlled study of the efficacy and safety of lenalidomide as maintenance therapy for high-risk patients with CLL following first-line therapy. The trial is ongoing and will provide information on the role of lenalidomide in the maintenance setting.

FCR therapy induces significant toxicity, predominantly neutropenia and infections, between one-fifth and one-quarter of patients treated with FCR will develop severe infections (Grade 3 or 4).[21] The issue of neutropenia is frequently being discussed; FCR induces more severe neutropenia at the beginning of treatment compared to FC. However, in the long-term this

Table 1. Addition of rituximab to fludarabine and cycleophosphamide: toxicities after the end of treatment (N=800).

Late neutropenias 2 months after end of treatment	N	%	p value
FCR	67	16.6	0.007
FC	35	8.8	
Late neutropenias 12 months after end of treatment	**N**	**%**	**p value**
FCR	16	3.9	0.7
FC	15	3.7	

Fischer K et al.[22]

toxicity appears to be neutralised[22] (Table 1). In addition, secondary malignancies following intensive chemotherapy (including FCR) occur. The CLL8 trial[22] showed that 13.1% of patients had secondary malignancies in the FCR arm compared with 17.4% in the FC arm (median time to onset 21.5 months [range 0-80], p=0.095). In future treatment concepts the issues that arise from chemotherapy should to be considered and if possible avoided.

In addition to FCR, the use of BR has been investigated in go-go patients in a Phase II trial.[11] The results of the trial showed an OR rate of 88.0% (95% CI 80.7-100.0%) with a CR rate of 23.1% and a PR rate of 64.9%. The side-effects that occurred were Grade 3 or 4 severe infections in 7.7% of patients and Grade 3 or 4 adverse events for neutropenia, thrombocytopenia and anaemia were documented in 19.7%, 22.2% and 19.7% of patients, respectively. These results indicate that there are fewer side-effects with BR than FCR, particularly the number of severe infections recorded. Nevertheless, it remains open to debate which therapy is more efficacious.

An analysis of the historic data of the results in Phase II trials[11,21] using FCR, FC or BR shows that PFS in patients treated with FCR was 77.6% versus 71.9% with BR and 63.9% with FC. In terms of OS there was negligible difference between the therapies (Table 2).

Table 2. Side-by-side analysis of progression-free survival and overall survival rates with fludarabine plus cyclophosphamide plus rituximab, fludarabine plus cyclophosphamide, and bendamustine plus rituximab.

Progression-free survival				
PFS	**pts, N**		**Median, months**	**24-months survival, %**
All patients	934	610 (65.3)	41.8	71.0
First-line treatment				
[1]CLL8	817	550 (67.3)	42.5	70.9
FCR	408	253 (62.0)	56.8	77.6
FC	409	297 (72.6)	32.9	63.9
[2]CLL2M BR	117	60 (51.3)	37.5	71.9
Overall survival				
OS	**pts, N**		**Median, months**	**24-months survival, %**
All patients	934	298 (31.9)	89.2	89.7
First-line treatment				
[1]CLL8	817	279 (34.1)	90.2	89.7
FCR	408	154 (37.7)	85.8	88.0
FC	409	125 (30.6)	NR*	91.3
[2]CLL2M BR	117	19 (16.2)	54.8	90.2

△5.7%

△1.1%

* Not reached

FCR: fludarabine plus cyclophosphamide plus rituximab; FC: fludarabine plus cyclophosphamide; BR: bendamustine plus rituximab; PFS: progression-free survival; OS: overall survival.

Hallek MH et al.[21]

Fischer K et al.[11]

A Phase III trial, CLL10 study, of the GCLLSG[25] evaluating first-line therapy of fludarabine, cyclophosphamide and rituximab in physically fit CLL patients without deletions of the short arm of chromosome 17 (del 17p) has achieved the core goal and the study has been closed. The data have been submitted to the American Society of Hematology (ASH) and it is hoped that the results of the trial will provide guidance on the best treatment for go-go patients in the future.

In the meantime, alternative therapy management is being considered, for example it may be possible to build on BR therapy for go-go patients. Consequently, the CLL2P trial[26] was initiated using lenalidomide in addition to BR but it was found that in this trial the combination was not feasible so the trial has been closed. Another suggestion is that the CD20 antibody is exchanged; the GCLLSG is planning the CLLR3 trial in which GA101 is used for maintenance. The patients will be randomised to one of two arms: fludarabine plus cyclophosphamide plus GA101 or bendamustine plus GA101. This trial will allow exploration of the use of the new CD20 in maintenance therapy. Furthermore, there are other new agents that are becoming available that inhibit the B cell receptor pathway, these new agents inhibit specific targets; fostamatinib targets spleen tyrosine kinase (SYK), PCI 32765 targets Bruton's agammaglobulinemia tyrosine kinase (BTK) and CAL-101 (GS-1101) targets phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit *delta* (PI3Kδ). Byrd et al.[27] assessed the safety and efficacy of ibrutinib, a BTK inhibitor, in patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL). The results showed that these high-risk patients with 17p or 11q deletion do not do as well in terms of PFS and OS compared with patients who have no 17p or 11q deletion. One way to intensify these small molecules for high risk and go-go patients is to add a CD20 agent. Burger et al.[28] found that the BTK inhibitor ibrutinib in combination with rituximab (iR) is well tolerated and displays profound activity in high-risk CLL patients. Initial data show that time to treatment failure of iR treated 17p deleted patients is improved compared with patients treated with chemoimmunotherapy alone. These results are from a short follow-up period and long-term data are required. The Helios trial[29] is an ongoing Phase III trial in physically fit patients with relapsed or refractory CLL or SLL evaluating BR plus ibrutinib versus BR plus placebo. It is expected that the results of this study will indicate whether the addition of a small molecule in the induction phase is of value for patients. However, the problem of resistance[30] has to be addressed. It is known from other TKIs used to treat chronic myeloid leukaemia that there are resistance problems; hence in the future the emergence of second and third generation TKIs for CLL may be seen.

Another approach to treatment of patients with CLL is to interfere with the apoptotic pathway. There are a group of drugs that target the B cell CLL/lymphoma 2 (BCL2) and are thus able to regulate apoptosis through the mitochondria; using ABT-199, a BCL-2 inhibitor, induces Bax/Bak activation by BH3 and stimulates the release of cytochrome-C to induce cell death. The use of ABT-199 has been trialled in a Phase I first-in-human study in patients with relapsed or refractory CLL.[31] The results showed a dramatic response in nodal size reduction in the majority of patients (n=51), median time to 50% reduction was 1.4 months (range 0.7-13.7) in a very short time period.

The future concepts of the GCLLSG include a number of Phase II trials for all-comers; these include go-go patients and unfit patients. The trials will use different combinations of drugs with an initial round of chemotherapy, and the GA101 antibody as maintenance, the proposed trials are:

- CLL2-BIG: Bendamustine followed by GA101 and ibrutinib; followed by ibrutinib and GA101 maintenance.
- CLL2-BAG: Bendamustine followed by GA101 and ABT-199; followed by ABT-199 and GA101 maintenance.
- CLL2-BCG: Bendamustine followed by GA101 and CAL-101; followed by CAL-101 and GA101 maintenance.

In addition, specific large Phase III trials are planned; the CLL13 trial is for go-go patients and is based on the CLL10 trial using BR and/or FCR. CLL13 will assess BR/FCR versus BR/FCR plus CC-292 (a BTK inhibitor) in patients with previously untreated CLL. The CLL14 trial will involve GA101 and ABT-199 followed by ABT-199 maintenance versus six cycles of GA101 + CLB in CLL patients with comorbidities.

The Economic Burden of CLL Treatment Now and in the Future

Dr George Follows

There are different views on how healthcare can be provided. In the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE) guidance supports healthcare professionals and others to make sure that the care they provide is of the best possible quality and offers the best value for money. In the USA there is a lot of debate about the Patient Protection Act and the Affordable Care Act; one view is *"The new health reform law -- the so-called Patient Protection and Affordable Care Act -- creates 159 new boards, commissions and agencies that will destroy the doctor-patient relationship and replace it with federal bureaucrats deciding who gets care and what treatments they can receive"* (Jason Millman). Politicians get very nervous about news headlines especially those which highlight the use of therapies in Europe that are not permitted in the UK, e.g. *'Betrayal of 20,000 cancer patients: Rationing body rejects ten drugs (allowed in Europe) that could extend lives'.*[32]

The UK works within a framework for calculating cost-effectiveness (NICE/Scottish Medicines Consortium [SMC]). The cost-effectiveness analysis is summarised using the expected incremental cost-effectiveness ratio (ICER);[33,34] this calculates the amount you have to spend to deliver a change in quality: ICER = change in costs/change in effectiveness. Change in effectiveness or clinical outcome is described using quality-adjusted life years (QALY);[33,34] the ICER is the cost of the treatment divided by QALY, this results in the extra years of life of given quality a person might gain as a result of treatment.[35] A very simplified example could be the following; a 60-year-old patient with acute myeloid leukaemia who would die without treatment has £100,000 spent to cure him and he lives 10 healthy years. Therefore, the patient's individual ICER is 10,000. However, if five patients are treated and only one survives then the overall ICER for the therapeutic intervention is 50,000. There is no doubt that society has to decide what it is willing to pay per QALY[33] and there will be a division (Figure 2)[36] in terms of balancing cost effectiveness and efficacy.

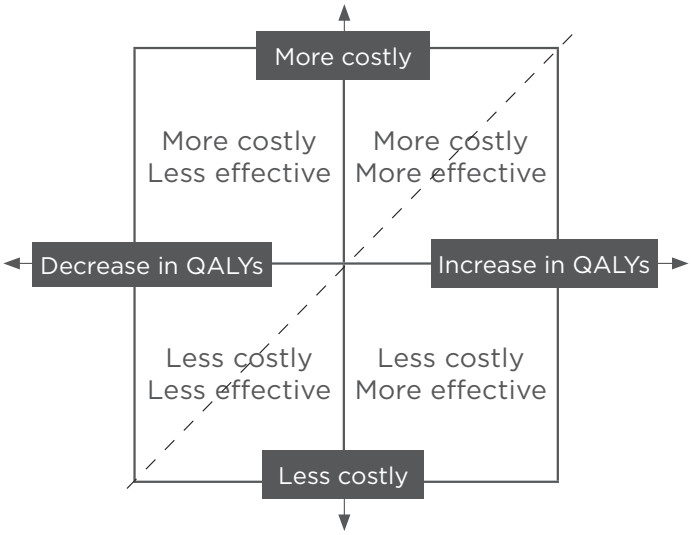

Figure 2. How do we decide on cost-effectiveness, i.e. society's willingness to pay for the quality-adjusted life year?
QALY; quality-adjusted life year.
NICE briefing paper.[33]
Image adapted from Laupacis A et al. [36]

The society's healthcare model will have to decide where it draws the line.

In the UK, the cost-effectiveness threshold of NICE/SMC indicates approximately £30,000 per QALY gained. There is continued debate about rarer conditions and orphan drugs; the EU legal definition of an orphan drug is the drugs used to treat a disease with the prevalence of <5 per 10,000 population. It is appreciated that drugs with orphan drug status increase the ICER, often the situation occurs where there is an ICER of >£30,000/QALY, but the treatment may still be defined as cost-effective, e.g. imatinib for the treatment of blast crisis chronic myeloid leukaemia with an ICER of £48,000, is the highest ICER for a treatment that has been approved in the UK. Special considerations are therefore given by the UK authorities where appropriate, e.g. the management of previously untreated conditions and 'ultra-orphan' drugs[37] (for conditions with a UK prevalence of <1 in 50,000).[38] This allows for greater expenditure to treat patients with 'ultra-orphan' drugs; for example for the treatment of Gaucher's disease (types I and III) with imiglucerase (Ceredase) has a preliminary estimated ICER of £391,244 per QALY in 270 patients in the UK.

Table 3. The present drug costs for chronic lymphocytic leukaemia regimens.

Regimen	Cycles of treatment	Line of treatment	Drug cost
Chlorambucil[i]	4.9	1st	£92
Bendamustine[i]	4.9	1st	£4,741
Fludarabine[ii]	6	1st	£2,812
Rituximab–fludarabine, cylophosphamide[ii]	6	1st	£12,940
Ofatumumab[iii]	12	Double refractory	£40,856*
Chlorambucil–rituximab[iv,v]	6	1st	£9,333
Bendamustine–rituximab[iv,v]	6	1st	£14,057

*Without patient access scheme

There are hugely difficult areas within pharmacoeconomics which include calculating the true cost of a regimen and what the true QALY gain for an intervention is; this can only be taken from trial data (PFS versus OS etc.) and trial patients do not necessarily represent the 'real world'.

The UK costs for CLL regimens (Table 3) range from chlorambucil which costs very little (£92) to current regimens with rituximab-fludarabine, cyclophosphamide (£12,940) or bendamustine–rituximab (£14,057).

It is not just the cost of the drugs that needs to be considered, there are additional aspects of care which include day unit time, supportive care drugs, short-term toxicities, additional investigations and longer-term toxicities. However, longer remissions equate to a better state of health, which potentially means fewer additional rounds of chemotherapy and improved QoL in remission which could potentially correlate with reduced broader healthcare costs. However, the standard of care, as defined by clinical trials does not mean this standard of care is applicable to all. A good example is FCR which is an international standard of care for CLL, but the patients recruited to the large randomised German CLL8 trial had a median age of 61 and an excellent performance status. We know from other large databases, such as the North of England Haematological Malignancy Research Network, that only a small percentage of patients are recruited into trials, and the age distribution of trial patients does not reflect the true age distribution of all patients. This highlights further that trial populations are often not representative of the 'real world'. This is the problem in clinical practice; if a pharmacoeconomic perspective is used and the ICER benefit is calculated for the use of FCR, this calculation is applicable to a 61-year-old with a median cumulative illness rating scale (CIRS) score of 0 or 1. Goede et al.[39] showed in the CLL8 trial that as comorbidities are accumulated the OS is reduced, raising the question of confidence in incremental cost-effectiveness ratio if the patient is unfit. The difficulty is that doctors are not actuaries, the aim is not to plan out the life expectancy of patients, but it does raise the question of survival. Across UK CLL trials (before the rituximab era) approximately one-third of patients had died within 4 years of starting first-line therapy. Of that third it is not known how many had died because of CLL and how many died because of their natural life expectancy. Should a patient's natural life expectancy influence decisions with regards to therapy? This is dangerous territory because in clinical practice if a patient, in actuarial terms, has a short life expectancy a cost economist would question the correctness of spending large amounts of money on cancer drugs. In practice this is the precarious domain of confusing age and comorbidity. As age increases people become survivors e.g. a woman in the UK who is 80 years old has a median survival of 9.1 years.[40] This would mean she would potentially have many years to benefit from novel therapies and if the person is fit it is likely that the median survival at 80 is more than 9.1 years.

The correlation that comorbidities will shorten life expectancy is not as straightforward as it appears. The Mayo clinic[41] evaluated their presenting CLL patients and found that the patients had a median of two comorbidities and half of them had a serious comorbidity. The assumption that the patients with a serious comorbidity would not survive as long as those without a serious comorbidity was difficult to prove within the data set. However, the data did show that if a patient was ineligible for a clinical trial, another marker of fitness, then there was a reduced survival rate. German data[42] from the CLL4 and

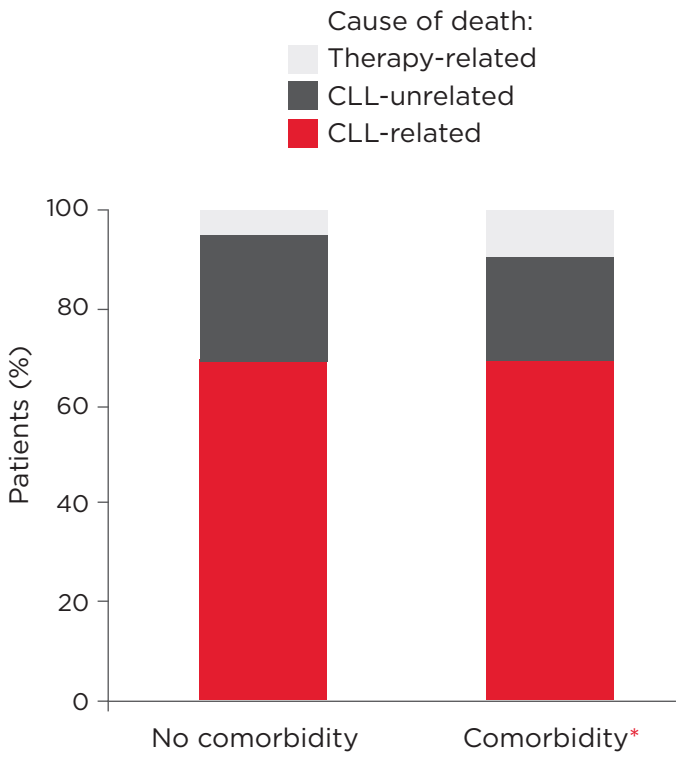

Figure 3. Comorbidities and life expectancy as presented by data from CLL4 and CLL5 trials. *Commonly Hypertension, Diabetes, Coronary Heart Disease.
Cramer P et al.[42]

CLL5 trials showed that at entry to the trials comorbidity was present in 53% of the patients and 25% had at least two comorbidities. PFS and OS were significantly shorter in comorbid patients (median OS 43.5 months versus 51.6 months; p=0.01; PFS was 20.3 months versus 23.5 months; p=0.03). The cause of death in these patients was analysed and the results showed that CLL-unrelated death which hypothetically should be higher in patients with comorbidities (commonly hypertension, diabetes and coronary heart disease) was actually similar to patients with no comorbidity (Figure 3).

A new era is on the horizon and consequently these are tremendously exciting times. However, this is causing huge disquiet, for example recently the UK press reported that: 'Of the 12 drugs approved by the Food and Drug Administration in the US in 2012, 11 were priced above $100,000 (£65,000) per patient per year. In addition the price of existing drugs of proven effectiveness has been increased by up to threefold.'[43] The cost of the novel agents to treat CLL is unknown as a monotherapy and novel agents used as a combination therapy will increase costs considerably.

In 2008 there were 2,798 patients diagnosed with CLL in the UK;[44] if a median 10-year life expectancy is assumed there are around 30,000 patients with CLL in the UK at any one time. If CLL management costs increase to £100,000 per patient per year when a patient is being treated with one or a combination of novel therapies, this will have a significant impact on funding. Assuming 50% of the patients will require treatment at some point, and 50% of the patients will be on therapy for 50% of their treatment lifetime, an approximate calculation would equate to £0.75 billion per year for the treatment of CLL. In addition there are ongoing costs; the current median survival for CLL patients is around 10 years. As survival increases with newer therapies, costs have the potential to increase disproportionately, as these patients will be surviving their CLL, and will begin to incur additional healthcare expenses of older age. The total NHS healthcare budget for England is £95.6 billion for 2013/2014; clearly the NHS cannot spend 0.5% of its budget on a single disease! This indicates that rationing will have to be implemented because there are inevitable cost limitations that will inhibit free access to these drugs in the UK healthcare environment.

There are issues that need to be addressed to enable the use of novel agents in the treatment of CLL. The science needs to be driven so that patient groups that will benefit most from the drug can be identified (e.g. will certain genomic subgroups of CLL benefit disproportionately from specific novel therapies). Clinical trials should be pushed to ascertain whether these novel agents can be used in a more intelligent way, to move away from ongoing therapy and towards different methods of treatment such as pulsed therapy and combinations that can shorten drug exposure. There is continued debate about what companies should be charging for the drugs. Their arguments for high prices reflect the research and development costs, nonetheless it has been suggested that more than research and development costs are being recouped. It is essential that companies are urged to keep costs down. These novel agents work but in the UK there will be a huge battle with funders. This is a very emotive topic, particularly when patients are in a relapsed refractory state and it

is known that they simply will not survive unless they can be treated with the new drugs; this situation will incite enormous pressure from the treating physicians on the funders to enable access to the necessary drugs. Therefore major challenges lie ahead for patients, clinicians and funding bodies alike.

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