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Maintenance therapy for chronic lymphocytic leukaemia (Protocol)

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[Intervention Protocol]

Maintenance therapy for chronic lymphocytic leukaemia

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effectiveness and safety of maintenance therapy in individuals with chronic lymphocytic leukaemia (CLL).

BACKGROUND

Description of the condition

Chronic lymphocytic leukaemia (CLL) is the most common lymphoproliferative disease in adults (Siegel 2015). The median age of diagnosis is 72 years (Eichhorst 2015) and the age-adjusted incidence is five per 100,000 person years (Howlader 2016; Statistics Canada 2016). CLL has a highly variable clinical course and prognosis (Hallek 2013a). Median overall survival (OS) varies from 18 months to over 20 years (Eichhorst 2015; Siddon 2013), and some individuals may lead a normal life with few or no symptoms for many years without requiring treatment. CLL is generally considered to be an indolent disease that progresses slowly with most individuals needing treatment only after years of clinical observation (watch and wait approach) (Hallek 2015). The severity of disease is reflected by the enlargement of the lymph nodes, liver, and spleen; an increased blood lymphocyte count; and impaired haematopoiesis (Binet 1981; Rai 1975). The two most widely used staging systems, proposed by Rai and colleagues (Rai 1975) and Binet and colleagues (Binet 1981), distinguish early (Rai K; Binet A), intermediate (Rai I, II; Binet B), and advanced (Rai III/IV; Binet C) stages of disease, which are characterised by substantial differences in clinical course and long-term survival. The current clinical staging systems are often of limited prognostic value at diagnosis, which happens usually at a time when most individuals are at an early stage of the disease (Binet 1981; Hallek 2008; Rai 1975). Recently, cytogenetic anomalies, including del(17p) deletions, somatic TP53 gene, and immunoglobulin variable heavy-chain mutations, have been found more effective in distinguishing more and less aggressive forms of CLL (Mertens 2014).

Most individuals with CLL are treated when they are at an advanced stage of the disease, and are symptomatic or have haematopoietic insufficiency (Hallek 2008). The standard of care for CLL has advanced rapidly from monotherapy with chlorambucil, bendamustine, or purine analogues (fludarabine, pentostatine) to combination-chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP); cyclophosphamide and vincristine with prednisolone (COP); or fludarabine with cyclophosphamide and to chemo-immunotherapy with fludarabine-based chemotherapy plus anti-CD20 monoclonal antibodies (mAbs) (rituximab) (Cramer 2016; Fischer 2012; Hallek 2010; Thompson 2016a). Recently, a number of novel drugs have enabled the targeting of key pathogenic pathways of CLL, including Bruton's tyrosine kinase (BTK), and phosphoinositide 3-kinase (PIK3) inhibitors that disrupt B cell receptor (BCR) signalling and venetoclax, an antagonist of the anti-apoptotic protein B-Cell Leukemia/Lymphoma 2 (BCL-2). B-cell receptor kinase inhibitors (BCRi) like Ibrutinib and Idelalisib are of benefit to older individuals (Burger 2014; Byrd 2013; Byrd 2014; Furman 2014; Jones 2017; O'Brien 2016; Zelenetz 2017). Most individuals with CLL respond to first-line therapy. Although durable and sustained remissions can be achieved, the majority relapse within five years of initial treatment (Shindiapina 2016; Wierda 2005). Patients who relapse frequently become resistant to treatment, develop fludarabine refractoriness and experience poor outcomes because the treatment options become limited and because of acquired genetic characteristics (un-mutated immunoglobulin heavy chain gene, 17p13 deletion, and TP53 mutations) in relapsed leukaemic clones, i.e. clonal evolution, with a poor prognosis (Dohner 2000; Grever 2007; Wierda 2017). Such individuals usually have significantly reduced OS because of early progression and poor response to salvage therapy (Cramer 2013).

The National Comprehensive Cancer Network guidelines recommend re-treatment with the regimen used as first-line therapy for individuals who require second-line treatment (Wierda 2017). However, fludarabine, cyclophosphamide, and rituximab (FCR) yields short remission times, and few previously treated individuals will have a complete response to treatment (Badoux 2011a; Robak 2010a; Wierda 2005). Second-line treatment with BCRi (Ibrutinib- or Idelalisib-) or B-cell lymphoma 2 inhibitor- (BCL-2i; venetoclax) targeted therapy leads to partial and sustained response in most individuals with refractory or relapsed disease, but complete responses with no minimal residual disease (MRD) are rare (Byrd 2014; Furman 2014; Thompson 2016b). As the progression-free period generally becomes shortened after each successive treatment period, novel strategies such as maintenance are needed to improve the depth and duration of the response to previous therapies. It has been proposed that maintenance therapy after chemo-immunotherapy might prolong the duration of remission by preventing the re-emergence of malignant CLL clones (Abrisqueta 2013; Wendtner 2004), and that maintenance regimens should be considered for individuals with high-risk CLL (Stilgenbauer 2010). In 2015, van Oers and colleagues (van Oers 2015), reported a significant improvement in progression-free survival (PFS) following ofatumumab maintenance in individuals with relapsed CLL in remission after re-treatment. That pilot trial was followed by other trials of maintenance therapy. In 2017, the CLLM1 (Fink 2017) and CONTINUUM (Chanan-Khan 2017) trials reported good outcomes with lenalidomide maintenance, and the CLL-2007-SA (Dartigeas 2018) and CLL-8a (Greil 2016) trials supported maintenance with rituximab. The GALACTIC trial, which is currently evaluating the maintenance effect of a novel anti-CD20 monoclonal antibody (obinutuzumab) began in 2017 (Oughton 2017). Despite the existence of maintenance therapeutic concepts, there is considerable debate about the efficacy and safety of this treatment modality (Oughton 2017). The maintenance choice currently depends on the frontline therapy used, presence of high-risk individual characteristics, and individual fitness (Grever 2007; Hallek 2017). There is an unmet need for methods to determine the optimal maintenance treatment to maximally improve clinically relevant outcomes in individuals with CLL after previous therapy. To summarise the available data and to provide discussion as to what the role of maintenance may be in the current treatment algorithms, we will perform a systematic review and pair-wise meta-analysis of all phase-3 randomised clinical trials (RCTs) comparing maintenance therapy regimens regarding to placebo/observation in individuals with CLL.

Description of the intervention

Many available treatment methods can effectively induce remission and improve PFS. Allogeneic stem-cell transplantation is the only potentially curative treatment for CLL (Dreger 2014), but as it is feasible in only a few individuals, prolonged PFS and OS are the realistic treatment goals for the majority of individuals. The current standard of care for younger individuals with CLL is frontline chemo-immunotherapy with regimens such as FCR (Hallek 2010; Thompson 2016b). BCRi such as Ibrutinib are frequently used in older individuals and in those individuals with relapsed disease (Byrd 2013). Intensifying FCR by adding drugs such as mitoxantrone (Faderl 2010) results in additional toxicity without improving therapeutic efficacy. Chemo-immunotherapy approaches still do not

achieve cure in the majority of individuals, with steady incidences of relapses observed, and until now, novel drugs do not appear to decreased rates of relapse, at least not in refractory or relapsed CLL, as evidenced by the necessity for treatment options after exhaustion of BCRi, a situation that remains a challenge (Jones 2018; Mato 2017; Thompson 2015), follow-up of frontline therapy trials using novel drugs, it is not yet clear, whether cure may be available in such settings. Conclusively, with the notable exception of CLL with better cytogenic prognosis (mutated IgVH and functional p53) treated with FCR, where there may be a fraction that might be cured (Thompson 2016b), CLL remains an incurable disease.

The objective of maintenance therapy, which follows induction or salvage therapy, is to prevent recurrence and to strengthen the effect of previous treatment. It is not an integral part of the standard treatment for CLL. Early on, chlorambucil was used as a treatment until progression strategy with trials using up to 12 months of chlorambucil treatment (Keller 1986; Montserrat 1985; Vidal 2016). However, the efficacy was very limited to achieve complete remissions even with prolonged treatment and close to 50% of individuals were progressive within one year (i.e. during projected treatment), suggesting a relatively rapid development of resistance (Vidal 2016). Anti-CD 52 antibody (alemtuzumab) maintenance was a subsequent attempt, long-term analysis of a phase 3 trial showed significant improvement of survival endpoints (Schweighofer 2009). However, severe drug related toxicities (especially increased opportunistic infections) rendered these advantages moot (Byrd 2009; Jones 2013; Kaufman 2011; Lin 2010; Wendtner 2004).

As antibody and immunomodulatory drug (IMiD) strategies became available, these were explored to counteract these problems. Some small phase-2 trials show that consolidation/maintenance treatment with lenalidomide (Chang 2016; Shanafelt 2013; Strati 2017), Rituximab (Abrisqueta 2013; Bo 2014; Del 2008; Foa 2014) are feasible. Following the development of a maintenance paradigm in other indolent lymphoma entities (Vidal 2017), initially a phase 2 trial which observed prolonged use of rituximab in CLLwas launched by Hainsworth and colleagues(Hainsworth 2003). Rituximab induction follow-up of four weekly courses of rituximab in six-monthly intervals as maintenance for two years achieved a median PFS of 18.6 months. Now, there are four major randomised trials exploring the maintenance role of anti-CD20 antibodies (Dartigeas 2018; Greil 2016; Robak 2018; van Oers 2015) in CLL. Clinical trials of IMiD lLenalidomide) (Chanan-Khan 2017; Fink 2017) have reported prolongation of PFS. Fink et al recruited individuals from this high risk group after 4 cycles of front-line FCR induction, by screening 468 individuals to randomise 89 individuals either Lenalidomide with ramp up dosing design or placebo. After a median follow-up of 17.9 months, lenalidomide showed a significant benefit for prolongation of PFS (hazard ratio : 0.168) (Fink 2017).

Novel target agents including BCRi (Ibrutinib and Idelalisib) and BCL-2i (venetoclax) are treating CLL with a strategy of treatment until progression. Phase-2 and -3 trials on the effect of Ibrutinib (Chanan-Khan 2016; Cramer 2018) and idealisib (Cramer 2018; Zelenetz 2017) on maintenance/consolidation are ongoing. Because maintenance therapy might preserve clinical or even molecular remission, omitting maintenance therapy could result in disease relapse, necessitating salvage therapy with high-dose chemotherapy, with or without autologous or allogeneic haematopoietic cell transplantation. Omitting maintenance therapy might ultimately result in a negative effect on the OS of individuals with CLL.

How the intervention might work

Maintenance therapy to improve the quality and duration of treatment response is practised in indolent lymphoma entities (Vidal 2017). CLL shares similar characteristics, and recent randomised phase-3 trials described below have reported significant benefits in PFS, but the evidence for improving OS requires more evidence (Beauchemin 2015). Maintenance and consolidation both prolong treatment with the intent of strengthening the response after post-remission treatment. Consolidation therapy is combined with induction treatment. Maintenance is a follow-up treatment to induction therapy intended to stabilise and deepen the response. In the clinical practice, these two therapeutic interventions are difficult to distinguish in individuals where neither approach has a curative effect regardless of intent. In this review, all post-remission interventions are considered “maintenance therapy”.

Anti-CD 52 antibody (alemtuzumab)

Alemtuzumab (Campath, MabCampath) is a humanised antibody specific for CD52, a surface protein expressed on B cells in both CLL and normal B and T cells (Wierda 2005). In a early phase-3 study, individuals with CLL in at least partial remission after front-line chemotherapy with either fludarabine or fludarabine plus cyclophosphamide were randomised to either maintenance treatment with alemtuzumab 30 mg three times per week for a maximum of 12 weeks or observation (Wendtner 2004). At 21.4 months of median follow-up, individuals receiving alemtuzumab had significantly longer PFS (24.7 months) than the controls, but the study was stopped because of unacceptable infectious toxicity. Following up surveillance reported five individuals given alemtuzumab achieved molecular remission, but all individuals in the control group had evidence of minimal residual disease (MRD). At a median follow-up of 48 months, individuals given alemtuzumab had significantly prolonged PFS compared with those who received observation (Schweighofer 2009). Despite toxicity, maintenance treatment with alemtuzumab induced molecular remission and reduced MRD that resulted in significantly improved long-term clinical outcome.

Immunomodulatory Drug (lenalidomide)

Lenalidomide is a 4-amino-glutamyl analogue of thalidomide that has clinical activity in CLL (Riches 2016). Lenalidomide has a unique mechanism of action, not only targeting cancer cells, but also modulating or interrupting multiple interactions of CLL cells and elements in their microenvironment (Acebes-Huerta 2014; Ramsay 2008; Wu 2008) that promote leukaemia or influence survival (Badoux 2011b; Chanan-Khan 2006 ;Chen 2011; Ferrajoli 2008). Its multifaceted mechanism of action and diverse effects on CLL cells have been reflected in improved immuno-surveillance outcomes (Kater 2014; Itchaki 2017). Two large RCTs reported significant prolongation of PFS of individuals with CLL who were given lenalidomide maintenance (Chanan-Khan 2017; Fink 2017). The CLLM1 study (NCT01556776) randomly assigned 89 individuals with CCL 2:1 to receive lenalidomide 5 mg maintenance or placebo. The hazard ratio (HR) for PFS was 0.16 (95% confidence interval (CI), 0.07 to 0.37) with a median follow-up of 17.9 months. Median PFS was not reached (95% CI, 32.3 to not evaluable) in the lenalidomide group and was 13.3 months (95% CI, 9.9 to 19.7) in the placebo group. However, study recruitment was stopped early because of poor accrual (Fink 2017). The global CONTINUUM study

(NCT00774345) found that maintenance therapy with lenalidomide prolonged PFS without affecting potential subsequent lines of therapy (Chanan-Khan 2017). In the CONTINUUM trial, eligible individuals had achieved complete or partial responses to second-line therapy and were randomly assigned to maintenance therapy with lenalidomide (160 individuals) starting at 2.5 mg/day with escalation to 5 mg or 10 mg as tolerated or to a placebo group (154 individuals). Lenalidomide reduced the risk of progression by more than half compared with placebo (HR, 0.40; 95% CI, 0.29 to 0.55), but no difference in OS was found during follow-up (Chanan-Khan 2017).

Anti-CD 20 antibody (rituximab, ofatumumab, obitumuzmab)

The CD20 antigen is present in more than 90% of B-cell lymphoma cells and is neither shed nor internalised after antibody binding (Tedder 1994), which makes it a target for immunotherapy with monoclonal anti-CD 20 antibody. Preclinical studies have shown that anti-CD20 activity includes complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and the induction of cell growth arrest and apoptosis (Li 2008; Li 2009; Teeling 2004). However, the increased occurrence of neutropenia and infections in individuals who received anti-CD20 has aroused concern (Greil 2016; Hallek 2010; Robak 2010b; van Oers 2015).

Rituximab

Rituximab is a genetically-engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. It has a synergic effect when administered in combination with chemotherapeutic agents used in standard first-line treatment regimens (Nabhan 2014). The immuno-chemotherapeutic combination regimen increases treatment efficacy compared with chemotherapy alone (Hallek 2017). Because of its benefit in induction therapy, the benefits of rituximab for maintenance therapy have been tested. Early data from small observational and uncontrolled, early-phase consolidation and maintenance trials suggest that maintenance therapy consisting of prolonged rituximab antibody therapy after use in induction can prolong disease-free survival (Abrisqueta 2013; Bo 2014; Del 2008 ;Foa 2014). The French Innovative Leukemia Organization conducted a multicentre phase-3 study that compared rituximab maintenance therapy versus observation to prolong PFS in individuals with CLL who were homogeneously treated with frontline FCR (Dartigeas 2018). After a median follow-up of 47.7 months, median PFS was longer in the Rituximab group (59.3 months) than in the observation group (49.0 months; HR 0.55, 95% CI, 0.40 to 0.75). Another phase-3 study (Greil 2016), randomly assigned 263 individuals in at least partial remission after first-line (80%) or second-line (20%) therapy to either two years of maintenance rituximab, or to observation. Rituximab maintenance significantly improved PFS (median 47.0 months versus 35.5 months; HR 0.50, 95% CI: 0.33 to 0.75), with no significant difference in OS. The median PFS achieved by FCR is three to seven years (Fischer 2016; Thompson 2016b), and evidence of MRD-related relapse in the peripheral blood emerges very early at a median of 12.0 months after chemo-immunotherapy. However, it was delayed to 31.3 months by rituximab maintenance (Greil 2016).

Ofatumumab

Ofatumumab is a human type I CD20 (IgG1-κ) monoclonal antibody, with potent in-vitro complement-dependent cytotoxicity even in rituximab-refractory cells (Barth 2012), a higher antibody-dependent cytotoxicity than rituximab (Rafiq 2013), and in-vivo efficacy in rituximab-refractory CCL (Wierda 2010)The PROLONG trial was a phase-3 study of ofatumumab maintenance in individuals with CLL in complete or partial remission after second-line or subsequent therapy (van Oers 2015). The individuals were randomised to two years of either ofatumumab or observation. Ofatumumab maintenance resulted in an improvement in PFS (median 29.4 months versus 15.2 months; HR 0.50, 95% CI, 0.38 to 0.66). There was no difference in OS.

Obitumuzmab

Obinutuzumab (formerly GA101) is a new generation humanised anti-CD20 mAbs with a type II glycoengineered Fc portion selected to increase its affinity for FcγRIIIa receptors on immune effector cells. The increased affinity for neutrophils and macrophages is intended to elicit enhanced antibody-dependent cellular cytotoxicity (Bologna 2011; Dalle 2011; Niederfellner 2011). As the cells targeted by obinutuzumab are B cells rather than other lymphocytes including T cells, obinutuzumab is likely to be significantly less immunosuppressive than alemtuzumab (Cartron 2014). The GALACTIC study (ISRCTN64035629) is an ongoing phase-2/-3, multicentre, randomised, open, parallel-group trial in previously treated individuals with CLL (Oughton 2017). The individuals were randomised to either obinutuzumab maintenance or observation. The phase-2 study will assess safety and short-term efficacy to screen responses eligible for continuing to the phase-3 study. The planned enrolment was 188 participants at 40 study centres in the UK (Oughton 2017).

BCR inhibitors (ibrutinib, idelalisib)

Novel target therapies including BCR inhibitors (ibrutinib, idelalisib), and BCL-2 inhibitor (venetoclax) have significantly changed the CLL treatment landscape. The BCR inhibitors Ibrutinib and Idelalisib have shown remarkable clinical activity in refractory or relapsed CLL across all risk groups, and have been approved by the FDA. (Brown 2018; Byrd 2014; Jones 2017; Roberts 2016 ;Seymour 2018; Zelenetz 2017).

Ibrutinib

Ibrutinib (Imbruvica), a covalent oral inhibitor of Bruton's tyrosine kinase, was approved by the US Food and Drug Asministration (FDA) for first-line and refractory or relapsed therapy for individuals with CLL (Brown 2018; Byrd 2014). The toxicities of BCR inhibitors both ibrutinib and idelalisib are well tolerated and usually self-resolving for most individuals with CLL, including fragile individuals. The notable adverse events of ibrutinib were increased bruising and incidence of atrial fibrillation.

Idelalisib

Idelalisib (GS-1101 or CAL-101) is an orally bioavailable, and selective tyrosine kinase inhibitor of the phosphatidylinositol 3-kinase (PI3K). PI3K isoform is essential for antigen-induced BCR signalling. Idelalisib combined with rituximab has shown benefit in individuals with refractory or relapse CLL as induction or salvage treatment (Furman 2014), and approved by the US FDA. The common adverse events are colitis, pneumonitis and liver function impairment. Except for the role as induction or salvage treatment, BCR inhibitors were also tested in subsequent maintenance therapy. However, most ibrutinib and idelalisib trials have used a treat-until-progression approach that makes distinguishing induction and maintenance phases difficult. Two trials have combined ibrutinib or idelalisib with bendamustin rituximab chemo-immunotherapy regimens in pretreated individuals (Chanan-Khan 2016; Zelenetz 2017),

and recently the German CLL study group proposed a "sequential triple-T concept" of targeted, tailored treatment aiming for total eradication of CLL (Cramer 2018; Hallek 2013b). In that approach, individuals with CLL would receive two cycles of bendamustine followed by induction and a maintenance treatment with CD20-antibody plus a BCR inhibitor. The CLL2-BIG trial (NCT02345863) evaluating ibrutinib and GA101 obinutuzumab), the CLL2-BCG trial (NCT02445131) evaluating idelalisib and obinutuzumab and the CLL2-BIO trial (NCT02689141) evaluating ibrutinib and ofatumumab have completed recruitment and analysis of the primary end point outcomes are under way (Cramer 2018; Seymour 2018).

BCL-2 inhibitor (venetoclax)

BCL-2, encoded in humans by the BCL2 gene, is the founding member of the Bcl-2 family of apoptosis regulator proteins, by either inducing (pro-apoptotic) or inhibiting (anti-apoptotic) cell death (Tsujimoto 1984). Dysregulation of BCL2 is associated with development of many haematological malignancies and resistance to treatment, and these regulatory pathways can now be therapeutically targeted. BCL-2 inhibitor (venetoclax) was approved by the US FDA in 2016 for the secondary-line treatment of individuals with CLL associated with 17p deletion.The recent Phase III MURANO trial reported the long-term outcome of venetoclax effect in individuals with refractory or relapsed CLL. Except venetoclax plus rituximab combination demonstrated superior PFS than conventional bendamustine plus rituximab (HR:0.16, 95%CI :0.12-0 to 23 of three-year PFS), the subsequent single maintenance venetoclax (400mg once daily) also yielded efficacious free of disease progression (one-year PFS:87.4%) (Seymour 2018).

Why it is important to do this review

Evidence available from published trials support maintenance therapy with anti-CD52 antibody, anti-CD20 mAbs, and IMiD (lenalidomide) as effective and well-tolerated options for individuals with CLL (Coiffier 2008; Hallek 2010; Robak 2010b). However, there are no systematic reviews assessing efficacy and safety as all available maintenance treatment of CLL has been published, and no maintenance therapy regimen has been proposed. This Cochrane Review will identify and summarise the available evidence regarding the impact of anti-CD 52 antibody, anti-CD 20 antibodies, IMiD, BCR inhibitors and BCL-2 inhibitor for maintenance treatment of individuals with CLL.

OBJECTIVES

To assess the effectiveness and safety of maintenance therapy in individuals with chronic lymphocytic leukaemia (CLL).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) with prospective identification of participants are eligible. Both full-text publications and abstracts will be evaluated if sufficient information is available on study design, participant characteristics, interventions, and outcomes. We will not impose any limitation with respect to the length of follow-up or language of publication. We will exclude studies that are quasi-randomised trials, cross-over trials, non-randomised trials, case reports, or clinical observations.

Types of participants

Trials including individuals with histologically-confirmed B-cell CLL are eligible. The study must have used the CLL diagnostic criteria specified by the 1989 and 2007 International Workshops on CCL, or the WHO classification of lymphomas (Binet 1981 ;Hallek 2008; Cheson 1996; Swerdlow 2016). We will include trials that enrolled individuals in at least partial haematological or molecular remission after previous treatment with randomisation to maintenance performed either before induction or after the achievement of partial remission. Trials including mixed populations, that is, individuals with different haematological malignancies, are eligible if data are available separately for the CLL cohort. If subgroup data for individuals with CLL are not provided in the publication, or after contacting the study investigators, the study will be excluded if less than 80% of individuals had CLL. There will be no age or disease severity limitation.

Types of interventions

All randomised trials of anti-CD52 antibody, anti-CD20 antibody, IMiD, BCR inhibitors or BCL-2 inhibitor given as maintenance/consolidation treatment in individuals in at least partial remission after previous treatment are eligible. Trials compared with either placebo or observation controls are eligible.

Experimental interventions

- Anti-CD 52 antibodies
- Immunomodulatory drugs
- Anti-CD 20 antibodies
- BCR inhibitors
- BCL-2 inhibitors

Comparator interventions

- Placebo/no intervention

Comparisons

- Anti-CD 52 antibodies versus placebo/no intervention
- Immunomodulatory drugs versus placebo/no intervention
- Anti-CD 20 antibodies versus placebo/no intervention
- BCR inhibitors versus placebo/no intervention
- BCL-2 inhibitors versus placebo/no intervention

Types of outcome measures

We will include all trials based on the inclusion criteria noted above, regardless of the reported outcomes and will estimate the relative differences in outcomes. The outcome measurements will be assessed based on the consensus guidelines published by International Workshop on CLL (iwCLL) for the design and conduct of clinical trials for individuals with CLL (Hallek 2018). For binary outcomes, if a study reports outcomes at multiple time points, we will use the latest reported time point in the meta-analysis. For time-to-event outcomes, data with the longest follow-up will be used if duplicate publications exist.

Primary outcomes

- Progression-freesurvival (PFS): defined as the time from study entry until objective disease progression or death. We will use the definitions of progression as defined in each trial. If PFS is

not available, we will use event-free survival defined as the time from study entry till progression, adverse event or death.

- Overall survival (OS): defined as the time from study enrolment until death from any cause.

Secondary outcomes

The following outcomes will be considered secondary.

- Treatment-related mortality (TRM): measured at any time after start of treatment and up to 28 days after discontinuation of the study treatment
- Complete response rate (CRR): measured at least two months after last treatment
- Overall response rate (ORR): measured at least two months after last treatment
- Minimal residual disease (MRD): level of MRD negativity that is clinically important is 0.01%—which is fewer than one CLL cell per 10.000 leukocytes. Measured at least two months after last treatment
- Grade 3 and 4 adverse events: defined by the common terminology criteria for adverse events (CTCAE 5.0) or as defined in the trial. Measured at any time after start of treatment and up to 28 days after discontinuation of the study treatment
- All adverse events
  : measured at any time after start of treatment and up to 28 days after discontinuation of the study treatment
- Treatment discontinuation: defined as treatment discontinuation from any cause at any time after participants were randomised to intervention/comparator groups.

Search methods for identification of studies

We will perform comprehensive searches without language restriction to reduce the possibility of language bias. We will use medical subject headings (MeSH) or their equivalent and normal text keywords as search terms. Searches will be tailored to individual databases and will be rerun withinsix6 months prior to anticipated publication of the review. All qualified studies will be included in the analysis.

Electronic searches

We will search the following databases and sources following the recommendations in Chapter 6 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011).

Databases of medical literature

- MEDLINE (1946 to present, via Ovid, see Appendix 1)
- Embase (1988 to present, see Appendix 2)
- The Cochrane Library including the Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), and Database of Abstracts of Reviews of Effects (DARE) (until present, see Appendix 3)

Clinical trial registries

- ClinicalTrials.gov (www.clinicaltrials.gov/, see Appendix 4)
- World Health Organization (WHO) International Clinical Trials Registry Platform search portal (who.int/trial search)
- EU clinical trials registry (www.clinicaltrialsregister.eu)

Searching other resources

Manual reference search

We will manually check the reference lists included in all eligible trials and in guidelines of retrieved review articles for further literature.

Personal contacts

We will contact experts in the field to retrieve other trials.

Other resources

We will identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved studies of various kinds such as included trials, reviews, meta-analyses, and health technology assessment reports. We will also contact study authors of included trials to identify any further studies that we may have missed. We will contact drug/device manufacturers for ongoing or unpublished trials. We will search abstracts in the proceedings of relevant professional societies published in the last three years if they are not included in CENTRAL. These include the American Society of Clinical Oncology (ASCO), American Society of Hematology (ASA), European Society of Medical Oncology (ESMO), and the European Hematology Association (EHA).

Data collection and analysis

Selection of studies

Two review authors (CHL and YFZ) will independently screen the abstracts of retrieved publications and decide whether to review the full text. In the case of disagreement the full text will be obtained for further discussion. The review will exclude studies that do not satisfy the inclusion criteria. Full-text copies of the remaining publications will be obtained. Two authors (CHL and YFZ) will independently read those studies and select relevant studies. In the case of disagreement, a third author (CLH) will review the study. We will include a PRISMA flow chart (Moher 2009) in the completed review to show the total number of retrieved references and the number of included and excluded studies. We will use reference management software (Endnote 2017) to identify and remove duplicate records and we will indicate the reasons for excluding studies that may have reasonably been expected to be included in the analysis in a table entitled “Characteristics of excluded studies”.

Data extraction and management

Two review authors (CHL and YFZ) will independently extract data using a form based on the standardised Cochrane data extraction form. If necessary, we will contact the authors of specific studies for supplementary information (Higgins 2011). If the review authors are unable to reach a consensus, we will consult a third review author (CLH) for the final decision. After agreement on the extracted data, we will enter the data into Review Manager 5 (Review Manager 2014).

We will extract the following information.

- General information: author, title, source, publication date, country, language, and duplicate publications.
- Quality assessment: sequence generation, allocation concealment, blinding (participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias.

- Study characteristics: trial design; study aims, setting, and dates; source of participants; inclusion/exclusion criteria; comparability of groups; subgroup analysis; statistical methods; power calculations; compliance with assigned treatment; length of follow-up; and time of randomisation.
- Participant characteristics: eligibility and recruitment method, baseline demographics including age, number of participants recruited/allocated/evaluated, disease status after first-line or previous treatment, participants lost to follow-up, and Rai/Binet stage.
- Interventions: drugs and dosages, administration route, frequency, and duration of maintenance and follow-up.
- Outcomes: definition and methods of measuring PFS, OS/mortality, complete/partial response rate, grades 3–4 adverse events requiring discontinuation of treatment, withdrawal rates including the number of individuals excluded from outcome assessment after randomisation and the reasons for their exclusion. If possible, we will extract data at the study-arm level, not the summary effects.
- Others: study sponsorship/funding, stated conflicts of interest of the investigators.

We will extract relevant outcomes data on an intention-to-treat basis as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we will attempt to obtain the numbers of events and the population totals for a two-by-two table. For continuous outcomes, we will obtain means and standard deviations or other data needed to calculate those estimates.

Potential effect modifiers

The following potential effect modifiers will be extracted from each study.

- Year of publication
- Type of anticancer drug used for previous treatment
- Intervention
- Population characteristics

Duplicate and companion publications

We will map all articles to unique trials and juxtapose all relevant data, to identify duplicate publications, companion records or multiple published reports of an identical trial.

Assessment of risk of bias in included studies

We will include a “Risk of bias” table for each included study as described in Review Manager 5 (Review Manager 2014). Two authors (CHL and YFZ) will independently assess each selected study for bias risk. We plan to resolve disagreements by group consensus or by consulting a third author (CL) for the final decision. We will assess the following criteria described in the*Cochrane Handbook for Systematic Reviews of Interventions,* Chapter 8 (Higgins 2011).

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other sources of bias

We will judge risk of bias domains as ‘low risk’, ‘high risk’ or ‘unclear risk’ and evaluate individual bias items as described in the*Cochrane Hand book for Systematic Reviews of Interventions* (Higgins 2011). We will evaluate the risk of performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessments) separately for each outcome. Outcomes will be grouped by subjective or objective measurement when reporting the findings in the Risk of bias' tables.

Objetive measurements: endpoints are not considered to be influenced by blinding.

- Overall survival/mortality
- Treatment discontinuation

Subjective measurements: endpoints are considered to be potentially influenced by blinding

- Treatment-related mortality (TRM)
- Complete response rate (CRR)
- Overall response rate (ORR
- Minimal residual disease (MRD)
- Progression-free survival (PFS)
- Adverse events: neutropenia, infection, renal or hepatic adverse events, and further adverse events

We will also assess attrition bias (incomplete outcome data) as an outcome-specific basis and present the result for each outcome separately in the 'Risk of bias' tables. The risk of bias will also be summarised across domains for each outcome in each included study and across studies and domains for each outcome as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). In the sensitivity analysis, we will compare trials with at least two criteria with high risk of bias with trials with none, or only one criterion, of high risk of bias.

Measures of treatment effect

The intention-to-treat results will be evaluated, and risk ratios (RRs) with their 95% confidence intervals (CIs) will be calculated for dichotomous data. We will use hazard ratios (HRs) with 95% CIs for analysis of time-to-event outcomes. Data with the longest follow-up will be used if duplicate publications exist. Mean differences (MDs) with 95% CIs will be calculated for continuous outcomes. If different instruments were used to assess in continuous treatment outcomes, we will estimate standardised mean differences (SMDs) with 95% CIs. For dichotomous outcomes, the planned units of analysis are the numbers of participants in the experimental and control arms. For continuous outcomes, the means with standard deviation and the number of participants in the experimental and control arms will be calculated.

Unit of analysis issues

The unit of analysis will be the individual participant. Should we identify cluster-randomised trials for inclusion in the review, we will handle these in accordance with guidance provided in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will exclude cross-over trials.

Dealing with missing data

Missing data will be accounted for as recommended in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will contact the authors of the included trials to request relevant missing data and additional information not reported in the trial publications. If the number of trial participants assessed for a given outcome is not reported, the number of participants randomised per treatment arm will be used as the denominator. For the binary outcomes, numerators will be used to calculate percentages if the absolute number of events is recorded. Missing means and standard deviation data will be accounted for as described in Chapter 7.7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and imputed as previously described (Furukawa 2006). If results are reported graphically, but not numerically, then the missing data will be estimated from figures. If not all randomised participants are included in the data that was evaluated, they will be assessed to determine whether the loss was random or nonrandom or could not be categorised. If the reasons for the data loss and the distribution across the study groups are not provided, the missing data will be considered unclear. We will perform sensitivity analysis of imputed results. We will evaluate the potential influence of missing data on the findings of the meta-analysis in the Discussion section.

Assessment of heterogeneity

Heterogeneity will be estimated by using the Chi^2 test and the I^2 statistic among the trials in each analysis. We will use a P value equal to 0.10 for the Chi^2 test for statistical significance and interpret the I^2 statistic as described in Chapter 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

- 0% to 40%, may not be important.
- 30% to 60%, indicates moderate heterogeneity.
- 50% to 90%, indicates substantial heterogeneity.
- 75% to 100%, indicates considerable heterogeneity.

If we identify substantial heterogeneity (I^2 > 50%), we will report it and explore possible causes by prespecified subgroup stratification by age, type of induction treatment, disease-risk group, allocation concealment, blinding, and study size a previously described (Deeks 2011). We will calculate the Tau^2 estimate of between-study variance in a random-effects meta-analysis. If excessive heterogeneity is not explained by subgroup and sensitivity analysis, the outcome results will not be pooled in the meta-analysis, but we will include a narrative description of the study results.

Assessment of reporting biases

We will report the potential reporting biases graphically in funnel plots and statistically test this by conducting a linear regression test for all outcomes if there are at least 10 trials included. Funnel plots of treatment effect will be compared with trial precision to illustrate asymmetry that indicates the potential for selection bias (e.g. the selective publication of trials with positive findings) (Egger 1997). Funnel plot asymmetry will be tested by linear regression analysis (Egger 1997). We will consider a P value less than 0.1 to be significant for this test (Sterne 2011).

Data synthesis

We will conduct data analysis as recommended in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). Data will be entered using the Cochrane Review Manager 5 statistical package (Review Manager 2014). We will summarise the data using both fixed-effect and random-effects models. We will use the random-effects model in the primary analyses and the fixed-effect model in sensitivity analyses. We will interpret random-effects meta-analyses with due consideration of the complete distribution of effects. In addition, we will perform statistical analyses based on the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We will calculate dichotomous outcomes by the Mantel–Haenszel method. For measuring continuous outcomes, we will use the inverse variance method. We will use generic inverse variance method for measuring time-to-event outcomes.

Quality of the evidence

To assess the certainty of the body of evidence for each outcome, we will use the GRADEprofiler Guideline Development Tool software (GRADEpro GDT 2015) to rank the quality of the evidence as described in *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; Schünemann 2017), which takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision and publication bias), but also issues related to external validity, such as directness of results. Three review authors (CHL, YFZ, and CL) will independently rate the quality of each outcome. Disagreements will be resolved by discussion or by a senior author (CLH).
We will downgrade the evidence from 'high' certainty by one level for serious (or by two levels for very serious) concerns for each limitation. Furthermore, we will explain decisions to downgrade the quality of studies in footnotes and will add comments to aid the reader's understanding of the review where necessary.

The evidence levels are detailed below.

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: we have limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Tabulated summary of findings

We will use the GRADE approach as described by the GRADE Working Group and summary our judgements in 'Summary of findings' tables. The following outcomes will be presented.

- Progression-free survival (PFS)
- Overall survival (OS)
- Overall response rate (ORR)
- Minimal residual disease (MRD)
- Treatment discontinuation
- All adverse events
- Grade 3 and 4 adverse events

For each comparison, we will demonstrate a summary of the evidence for the main outcomes in a 'Summary of findings' table, which will provide key information about the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies, numbers of participants and studies addressing each important outcome and the rating of the overall confidence in effect estimates for each outcome (Guyatt 2011; Schünemann 2017).

Subgroup analysis and investigation of heterogeneity

The following variables will be included in subgroup analyses to determine any source of heterogeneity. Furthermore, we will explore potentially important clinical characteristics by stratifying the primary outcomes by the individual subgroups as given below.

- Age (adults < 70 versus adults ≥ 70 years of age)
- Type of comparator protocol (placebo or observation)
- Rai and Binet disease stage (B or C)
- Response to induction (partial or complete responses)
- Influence of prognostic factors (TP53 mutation, 17p-deletion or immunoglobulin heavy-chain variable region gene mutation)
- When maintenance therapy was given (first-line or treatment of previously treated individuals)
- Differences in prior treatment regimens (only alkylating monotherapy or chemo-immunotherapy)

Differences between subgroups will be assessed with the Chi^2 test (Deeks 2011).

Sensitivity analysis

The robustness of the results will be tested with fixed-effect pairwise meta-analysis. The sensitivity analysis will use the component quality method including low and high risk of bias (see: Assessment of risk of bias in included studies). Variables will potentially include allocation concealment (Schulz 1995), blinding (individuals, caregivers and assessors), randomisation method, incomplete outcome data (adequately, inadequately addressed), selective reporting (Higgins 2011), definitions of OS and PFS (randomisation to maintenance or other time point) and the type of publication (full paper, abstract, unpublished data).

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APPENDICES

Appendix 1. MEDLINE OVID search strategy

1. exp LEUKEMIA, B-CELL/
2. exp LEUKEMIA, LYMPHOCYTIC, CHRONIC, B-CELL/
3. ((leuk?em$ or leu?em$ or lymph$) adj (lymphocyt$ or lymphoblast$ or linfoid$ or b-cell$)).tw,kf,ot.
4. (chronic$ or cronic$ or chroniq$ or well-differential$).tw,kf,ot.
5. 3 and 4
6. cll.tw.
7. 1 or 2 or 5 or 6
8. exp MAINTENANCE/
9. maintenanc$.tw,kf,ot.
10. ((post-remission$ or postremission$) adj2 therap$).tw,kf,ot.
11. or/8-10
12. 7 and 11
13. exp ANTIBODIES, MONOCLONAL/
14. (antibod$ adj2 monoclonal$).tw,kf,ot.
15. exp LENALIDOMIDE
16. 13 or 14 or 15
17. exp ANTIGENS, CD20/
18. ((CD20 or CD-20 or CD 20) adj3 antibod$).tw,kf,nm,ot.
19. (ANTI-CD20 or ANTI CD20).tw,kf,ot,nm.
20. (ANTICD20 or ANTI-CD-20 or ANTICD-20).tw,kf,nm,ot.
21. mabt$.tw,kf,ot,nm.
22. ritux$.tw,kf,ot,nm.
23. ofatumumab$.tw,kf,ot,nm.
24. arzerr$.tw,kf,ot.
25. obinutuzumab$.tw,kf,ot.

26.gazyva$.tw,kf,ot.
27.exp ANTIGENS, CD52/
28.((CD52 or CD-52 or CD 52) adj3 antibod$).tw,kf,ot,nm.
29.(ANTI-CD52 or ANTI CD52).tw,kf,ot,nm.
30.(ANTICD52 or ANTI-CD-52 or ANTICD-52).tw,kf,ot,nm.
31.alemtuzumab$.tw,kf,nm,ot.
32.campath$.tw,kf,nm,ot.
33.lenalidomide$.tw,kf,nm.
34.revlimid$.tw,kf,ot,nm.
35.or/17-34
36.12 and (16 or 35)
37.randomized controlled trial.pt.
38.controlled clinical trial.pt.
39.randomized.ab.
40.placebo.ab.
41.drug therapy.fs.
42.randomly.ab.
43.trial.ab.
44.groups.ab.
45.or/37-44
46.36 and 45
47.humans.sh.
48.46 and 47

Appendix 2. Embase search strategy

1. exp B CELL LEUKEMIA/
2. exp CHRONIC LYMPHATIC LEUKEMIA/
3. ((lymphocyt* or lymphoblast* or b-cell*) adj (leukemia*)).tw.
4. (chronic* or well-differential*).tw.
5. 3 and 4
6. cll.tw.
7. 1 or 2 or 5 or 6
8. exp MAINTENANCE/
9. maintenanc*.tw.
10. ((post-remission*) adj2 therap*).tw.
11. or/8-10
12. 7 and 11
13. 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR (random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer*):de,ab,ti
14. 12 and 13
15. exp ANTIBODIES, MONOCLONAL/
16. (antibod* adj2 monoclonal*).tw.
17. exp LENALIDOMIDE
18. 15 or 16 or 17
19. 14 and 18
20. exp ANTIGENS, CD20/
21. ((CD20 or CD-20 or CD 20) adj3 antibod*).tw.
22. (ANTI-CD20 or ANTI CD20).tw.
23. (ANTICD20 or ANTI-CD-20 or ANTICD-20).tw.
24. mabt*.tw.
25. ritux*.tw.
26. ofatumumab*.tw.

27.arzerr*.tw.
28.obinutuzumab*.tw.
29.gazyva*.tw.
30.exp ANTIGENS, CD52/
31.((CD52 or CD-52 or CD 52) adj3 antibod*).tw.
32.(ANTI-CD52 or ANTI CD52).tw.
33.(ANTICD52 or ANTI-CD-52 or ANTICD-52).tw.
34.alemtuzumab*.tw.
35.campath*.tw.
36.lenalidomide*.tw.
37.revlimid*.tw
38.or/20-37
39.19 and 38

Appendix 3. Cochrane Central Register of Controlled Trials search strategy

1. MeSH descriptor Leukemia, B-Cell explode all trees
2. MeSH descriptor Leukemia, Lymphocytic, Chronic, B-Cell explode all trees
3. (lymph*) OR (leu*em*):TI,AB,KY
4. (lymphoblast*) OR (lymphocyt*) OR (linfoid*) OR (b-cell*):TI,AB,KY
5. (chronic*) OR (cronic*) OR (chroniq*) OR (well-differential*):TI,AB,KY
6. CLL
7. (#1 OR #2 OR #3 OR #4 OR #5 OR #7)
8. Mesh descriptor Maintenance explode all trees
9. maintenanc* OR (post-remission*):TI,AB,KY
10. (#8 OR #9)
11. (#7 AND #10)
12. MeSH descriptor Antibodies, Monoclonal explode all trees
13. MeSH descriptor Antigens, CD20 explode all trees
14. (CD20) OR (CD-20) OR (CD 20) OR (ANTI-CD20) OR (ANTI CD20) OR (ANTICD20 OR (ANTI-CD-20) OR (ANTICD-20):TI,AB,KY
15. (antibod*) OR (monoclonal*):TI,AB,KY
16. (mabt*) OR (ritux*):TI,AB,KY
17. (ofatumumab*) OR (arzerr*):TI,AB,KY
18. (obinutuzumab*) OR (gazyva*):TI,AB,KY
19. MeSH descriptor Antigens, CD52 explode all trees
20. (CD52) OR (CD-52) OR (CD 52) OR (ANTI-CD52 or ANTI CD52) OR (ANTICD52 or ANTI-CD-52 or ANTICD-52):TI,AB,KY
21. (alemtuzumab*) OR (campath*):TI,AB,KY
22. (lenalidomide*) OR (revlimid*):TI,AB,KY
23. (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)
24. (#11 AND #23)

Appendix 4. ClinicalTrials.gov search strategy

Search Terms: (chronic lymphocytic leukemia OR B-cell leukemia) AND (maintenance OR consolidation)

CONTRIBUTIONS OF AUTHORS

Cho-Hao Lee wrote the protocol.
Chin Lin designed the data input methods.
Tzu-Chuan Huang contributed clinical expertise.
Yi-Ying Wu contributed clinical expertise.
Yi-Fen Zou developed the search strategy.
Ju-Chun Cheng designed the content input methods.
Ching-Liang Ho wrote the protocol.

DECLARATIONS OF INTEREST

None of the authors are aware that they have any conflicts of interest.

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