BHS guidelines for the treatment of chronic lymphocytic leukaemia anno 2012

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Tremendous improvements in treatment outcome have been obtained over the past decade but for most of the patients chronic lymphocytic leukaemia (CLL) still remains an incurable disease. We eagerly await tools incorporating patient related, disease related and treatment related factors, in order to balance efficacy and toxicity and to personalise treatment in a more rational manner. No treatment is necessary for patients without active and/or advanced disease, regardless of prognostic factors. When treatment is indicated we recommend fludarabine, cyclophosphamide, rituximab (FCR) as front-line strategy for fit patients, bendamustine, rituximab (BR) for patients unfit for FCR and chlorambucil for older patients with a geriatric profile or patients with major comorbidities or a reduced performance status. The choice of treatment for patients with recurrent advanced and/or active disease depends on the duration of response to the previous treatment and on the type of treatment refractoriness. Reduced intensity conditioning allogeneic stem cell transplantation should be considered for patients with a de novo or an acquired 17p deletion, for patients refractory to F, or F and alemtuzumab, or for patients with an early relapse after chemo-immunotherapy.

We encourage patients to enter clinical trials exploring new agents. Among these new approaches, the signal transduction inhibitors have shown remarkable activity in very advanced disease, independent of genetic aberrations.

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Introduction

The Belgian Hematological Society (BHS) Lymphoproliferative Working Party reviewed the recent literature on treatment of chronic lymphocytic leukaemia (CLL) to make recommendations on the best strategies for front-line and subsequent-line treatment and for treatment of Richter transformation and autoimmune complications. The members are aware that some treatment options although efficacious and safe, are waiting for label prescription and/or reimbursement.

Incidence

CLL is the most common form of adult leukaemia in Western countries with an incidence of 3.8 per 100,000 person-years.[1] CLL occurs twice as often in males as in females and is most common in the Caucasian population.[2] CLL is primarily a disease of the elderly. Sixty-five to 70% of patients are 65 years or older at diagnosis with a median age of seventy-two years.[1,2]

Diagnosis

The diagnosis of CLL requires the presence of at least 5000/μl B lymphocytes in the blood for the duration of at least three months. Morphologically, the CLL cells are small, round cells with a narrow border of cytoplasm and a dense nucleus with clumped chromatin and indiscernible nucleoli. Gumprecht shadows or smudge cells are frequently seen. Clonality of the B cells (kappa or lambda immunoglobulin (ig) light chains) needs to be confirmed by flow cytometry.[3] Typically, CLL cells co-express the T cell antigen CD5 with B cell antigens. CD19 and CD23 show a strong expression whereas surface ig, CD20 and CD79b are only weakly expressed compared to normal B cells. The immunophenotypic scoring system defined by Moreau et al. is useful to differentiate CLL from other leukaemic lymphomas (CLL score ≥ 3: diagnosis of CLL definitely, CLL score ≤ 2: diagnosis of CLL unlikely, except for some cases with trisomy 12 who could show also an atypical morphology).[4] Bone marrow biopsy is not required for diagnosis.

The term small lymphocytic lymphoma (SLL) is used for patients with lymphadenopathy and/or splenomegaly but with <5000/μl B lymphocytes in the peripheral blood and no cytopenias due to bone marrow infiltration. The diagnosis of SLL, when possible, should be confirmed by histopathology of a lymph node biopsy.[3]

In the absence of lymphadenopathy, organomegaly, cytopenia and clinical symptoms, the presence of <5000/μl B lymphocytes in the peripheral blood with a CLL phenotype is defined as monoclonal B-lymphocytosis (MBL)-CLL type.[3]

Clinical presentation

Patients with CLL are generally asymptomatic at presentation, and the diagnosis is often made incidentally when lymphocytosis is noted at the time of a routine blood evaluation. At diagnosis, one quarter of patients reveal lymphadenopathies, approximately 15% organomegaly while B symptoms are noticed in only 5%.[5,6]

The clinical course of CLL is highly variable. One third of CLL patients never require treatment, another third show disease progression after an initial indolent phase and the remaining third exhibit an progressive disease from the onset and need immediate treatment.[7]

Staging

The two widely used staging systems are the Rai (used primarily in the United States) and the Binet (used in Europe). These clinical staging systems are based on physical examination and complete blood cell counts alone. The value of each system lies mainly in its prognostic implications for survival.[8-10] Today 80% of the newly diagnosed patients are staged as Binet A, ± 13% as Binet B and ± 7% as Binet C.[6] With the new treatment options, patients with the most advanced stage (Rai 3-4, Binet C) have now a predicted survival time of approximately six years in contrast with one to two years at the time of publication of these staging systems.[6,8-11]

Risk stratification

Clinical staging systems as Rai and Binet remain good prognostic factors, but at diagnosis they cannot identify patients with indolent or progressive disease and are not able to predict response to treatment.

Factors like age, gender, performance status, lymphocyte count, lymphocyte doubling time (LDT), lymphocyte morphology, degree and pattern of bone marrow infiltration, lactate dehydrogenase (LDH), β2-microglobulin, serum thymidine kinase, conventional karyotyping, immunophenotype, sCD23, chromosomal aberrations identified by fluorescence in situ hybridization (FISH) analysis in a few recurrent regions

(13q, 11q, 17p deletion and trisomy 12), the mutational status of immunoglobulin heavy chain variable region genes (IGVH), CD38 and zeta-chain-associated protein of 70kDa (ZAP-70), have been reported to correlate with disease progression, duration of response and/or survival. As clonal evolution is a common phenomenon during the disease, FISH (especially 11q and 17p deletion) should be performed or repeated before initiation of therapy.[13]

Several investigators have tried to develop models incorporating some traditional and new prognostic markers to identify patients at high risk for progression to treatment and shorter survival. The Mayo Clinic CLL database showed that prognostic tests as FISH and IGVH had little utility for predicting OS independent of stage among patients ≥ 75years although they were useful for predicting time to first treatment (TTFT).[14]

Indications for initiation of treatment

In 2008, the International Workshop on Chronic Lymphocytic Leukemia updated the guidelines established by the 1996 National Cancer Institute Working Group for the initiation of treatment.[3]

Criteria for initiating first-line or second-line treatment follow similar rules.

Newly diagnosed patients with asymptomatic disease (Rai 0-2 or Binet A-B) should be monitored without treatment unless they have evidence of active disease. The treatment should be reserved for patients with advanced disease (Stage Rai 3-4 or Binet C) and/or active disease which is defined as:

Disease progression

- Lymphocyte doubling time of <6 months or increase of >50% over a 2-month period if lymphocyte count ≥30000/μl initially
- Massive (≥6 cm below costal margin) or progressive or symptomatic splenomegaly
- Massive (≥10cm) or progressive or symptomatic lymphadenopathy
- Progressive marrow failure leading to cytopenia

Autoimmune anemia or thrombocytopenia poorly responsive to corticosteroids

Disease related symptoms

- 10% weight loss in six months
- Extreme fatigue (ECOG PS ≥2)
- Fever >38°C for >2 weeks without infection
- Night sweats >1 month without infection

Treatment

Before initiating treatment consideration must be given to:

- Patient related factors such as age, PS, comorbidities and patient wishes
- Disease related factors such as the presence of adverse prognostic factors
- Treatment related factors such as expected degree and duration of response, contraindications to and side-effects from particular treatment modalities

Treatment for early and non-active disease is not recommended regardless of prognostic factors.[3] The role of early intervention versus deferred treatment in patients with high risk disease (11q or 17p deletion, unmutated IGVH, …) is currently under investigation in randomised controlled trials (RCTs) (German CLL Study Group (GCLLSG) CLL7: FCR vs wait and see, Cancer and Leukemia Group B (CALBG) 10501: FR vs wait and see (closed because slow accrual)).

Frontline treatment of advanced and or active disease in 'Fit' patients

Fludarabine (F) is the most extensively studied purine analog for the treatment of patients with CLL. Pentostatin and cladribine are other purine analogs used in the treatment of CLL. In an attempt to achieve synergism and increase response rates, purine analogs and alkylating agents have been studied in combination due to their different mechanisms of action and toxicity profiles. Fludarabine plus cyclophosphamide (FC) is the most thoroughly studied chemotherapy combination for CLL. Treatment with this combination improves overall response (OR), complete response (CR), and progression free survival (PFS). However, OS was not significantly increased.[15-17]

FCR chemoimmunotherapy (CIT) with F (25mg/m^2 d1-3), C (250mg/m^2 d1-3), rituximab (R) (Cycle 1 375mg/m^2, from cycle 2 500mg/m^2) (q4wks, up to six cycles) should be the standard first-line therapy in patients, who are fit, have no major comorbidities and a normal renal function (creatinine clearance ≥70 ml/min). This CIT (FCR versus FC) achieves the best possible response (OR 95,1 vs 88,4%, CR 44,1 vs 21,8%) with prolonging of median PFS (51,8 vs 32 months (mo)) and also OS (3y) (87 vs 83%). Especially patients with an 11q deletion and unmutated IGVH fare better when treated with FCR.[18] However because FCR is more toxic than F or FC, a risk of prolonged cytopenia and treatment

related myeloid neoplasms exist a search for less toxic alternatives is ongoing (FCR versus BR (GCLLSG CLL 10), FCR versus FR (CALGB 10404)). A French-Belgian phase 3 RCT compared FCR versus FC-alemtuzumab (A) (30 mg d1-3 sc, q4wks, up to 6 cycles) in untreated CLL patients with active disease and without a 17p deletion. Recruitment was halted prematurely due to an excess of toxicity in the FCA-arm (infections, lymphomas) although responses and OS were identical.[19]

Frontline treatment of advanced and/or active disease in 'Unfit' patients

Bendamustine (B) (100 mg/m^2, d 1-2, q4wks, up to 6 cycles) has been approved for frontline treatment of patients with advanced CLL, not fit for FCR (compromised renal function, Cumulative illness rating scale (CIRS) >6, hemolytic anemia, infectious risk, …). Bendamustine offers a higher response rate and a longer PFS than chlorambucil (Chl) (21.2 vs 8.8 mo) with manageable toxicity. The median time to next treatment (TTNT) was significantly longer for patients treated with B (31.7 vs 10.1 mo). So far there is no difference in OS although patients showing any response had a longer survival than non-responders. This trial confirms that B offers greater efficacy than Chl without compromising quality of life, even in the elderly.[20,21] Rituximab (R) in combination with any chemotherapy has been approved by the European Medical Agencies for frontline treatment since 2009. **BR** (B 90 mg/m^2, d 1-2, R Cycle 1 375mg/m^2, from cycle 2 500mg/m^2, q4wks, up to 6 cycles) increases OR and median PFS (88%, 34 mo) compared to B monotherapy in an historical control (68%, 22 mo). Since the major advantage of the BR combination is reduced toxicity compared to FCR, this regimen may be particularly suitable for treatment of elderly patients or those with multiple comorbidities.[22]

In elderly patients with a geriatric profile or patients with significant comorbidities or a reduced PS, the goal of treatment should be palliation while keeping a minimal toxicity. **Chlorambucil** (Chl) is here still a good treatment option due to its oral availability, low incidence of adverse effects and minimal cost. RCTs comparing Chl versus F, B or A showed a lower OR and a lower PFS compared to the comparator, however without a loss of survival.[20,21,23,24] Phase 2 trials have shown that R added to Chl is effective with an acceptable tolerability.[25,26] Results of phase 3 trials combining anti-CD20 monoclonal antibodies and Chl are awaited (Chl vs Chl+ Ofatumumab (OMB110911), Chl vs Chl+ R vs Chl+ Obinutuzumab (GA-101) (GCLLSG CLL11)).

Lenalidomide is another promising oral drug in elderly patients with CLL. A phase 2 trial in patients older than sixty-five showed an OR of 60% with a CR of 10% and an estimated 2y PFS of 60%. Gradual dose-escalation seems necessary to control tumour flare reactions. The other predominant toxicity associated with lenalidomide was myelosuppression.[27] A phase 3 RCT comparing lenalidomide and Chl is ongoing.

Frontline treatment of advanced and/or active disease in CLL patients with 17p deletion or TP53 mutations

Patients showing a 17p deletion or a *TP53* mutation are poor responders to conventional treatment (chemotherapy, immunotherapy, CIT, corticosteroids). **Alemtuzumab** has been licensed and reimbursed in Belgium for CLL patients with active disease and 17p deletion as frontline treatment. The phase 2 National Cancer Research Institute (NCRI) CLL 206 trial evaluated efficacy and safety of A and methylprednisolone in 17 untreated CLL patients with *TP53* defects. The OR, CR, median PFS and median OS were 88%, 65%, 18.3 and 38.9 mo, respectively, making this combination the most effective induction regimen reported in *TP53* deleted CLL.[28]

Allogeneic stem cell transplantation (SCT) should be considered as a reasonable therapeutic option for younger, healthy patients with deletion 17p or *TP53* mutations who require treatment and achieve a response after induction treatment according the recommendations of the European group for blood and bone marrow transplantation (EBMT).[29]

Second or subsequent-line treatment

Second or subsequent-line treatment should depend again on patient and disease related factors. Important treatment related factors to consider are type of prior treatment and the duration of response to that treatment. First-line treatment can be repeated if the duration of response has lasted more than one year following chemotherapy or two years following CIT. These patients are considered treatment sensitive.[3]

Refractory CLL has been defined as no response or response lasting less than six months from last therapy. However patients with suboptimal (no CR) or short response (<24 mo) after CIT or SCT also have a poor outcome despite salvage strategies.[30]

According to the REACH trial comparing FC and FCR in relapsed CLL, previously treated with Chl or F, **FCR** was superior to FC regarding OR (70 vs 58%), CR (24 vs 13%), median PFS (30,6 vs 20,6 mo) and duration of response (39.6 vs 27.7 mo). Overall survival however was not different.[31] The MDACC group showed that patients relapsing after alkylating agents, F, R, FC or another F combination respond equally well to FCR.[32] However, FCR in this setting is not without toxicity (neutropenia, infections, second neoplasms) and its use is most appropriate for fit patients.[32,33]

Bendamustine appears to be a good choice for second or subsequent-line treatment due to the lack of significant cross-resistance with alkylating agents and fludarabine. In a phase 2 trial **R added to B** (B 70 mg/m^2 d1-2, R cycle 1 375 mg/m^2, from cycle 2 500 mg/m^2, q4wks, up to six cycles) was effective (OR 59%, CR 9%, median PFS 15,2 mo, median OS 33,9 mo) and safe even in patients refractory to fludarabine (OR 45,5%). OR was equal for patients younger or older than seventy. Patients with a 17p deletion however, did not benefit from this treatment regimen.[34]

Alemtuzumab has been licensed and reimbursed in Belgium for the treatment of F-refractory patients. Responses were observed in all prognostic subgroups especially when the disease was confined to the blood and the bone marrow. Patients with bulky lymphadenopathy (>5 cm) respond less well.[35,36] Recent studies have shown that subcutaneous administration of A may be equally effective and less toxic as the intravenous route.[36] The occurrence of serious infections in F-refractory patients is a concern after salvage treatment. However the infectious risk with A was not higher than with FC combinations or anthracycline-containing regimens in this particular CLL population. CMV reactivation and CMV disease is an infectious complication typically seen during treatment with A. A high grade of suspicion and prompt treatment can avoid life-threatening complications.[37]

A phase 3 RCT comparing **FA** (F 30 mg/m^2, A 30 mg d1-3, q4wks, up to six cycles) vs F (F 25 mg/m^2 d1-5, q4wks, up to six cycles), tested the hypothesis that FA might improve the outcome of CLL patients with relapsed or refractory disease. FA was superior to F regarding CR (13 vs 4%), PFS (23,7 vs 16,5 mo) and OS (median not reached vs 52,9 mo) leading to the conclusion that FA is another treatment option for previously treated CLL.[38] **FCA** (F 25 mg/m^2, C 200 mg/m^2, A 30mg d1-3, q4wks, up to six cycles) in a multicentre phase II trial in CLL patients with relapsed or genetic high risk CLL , leads to OR and CR rates of 68 and 22%.[39] At the MDACC investigators tried to improve FCR by adding A. **CFAR** (C 250 mg/m^2 and F 25 mg/m^2 d3-5, A 30 mg IV d1-3-5, R cycle 1 375 mg/m^2, from cycle 2 500 mg/m^2 d2, q4wks, up to 6 cycles) given to relapsing and refractory CLL patients induced an OR of 65%, a CR of 29% with a median OS and time to progression of 16,7 and 10,6 mo. Although CFAR produced good response rates in this highly pretreated group of patients no benefit in PFS and OS was seen.[40]

Steroids reduce bulky lymphadenopathies, cause less myelosuppression than alkylating agents and purine analogs and kill lymphoid cells by a p53-independent mechanism. **Rituximab** (375mg/m^2/w/4w) combined with **high dose methylprednisolone** (HDMP) (1g/m^2 d1-5, q4wks up to 3 cycles) in F-refractory patients showed an OR rate of 93% and a CR of 36%. Time to progression was 15 mo and median TTNT 22 mo. A high response rate was seen in patients with high-risk cytogenetic aberrations (11q and 17p deletion).[41] Another promising approach is the combination of **high-dose corticosteroids** (HDMP 1g/m^2 d1-5 q4wks, dexamethasone 40mg d1-4 q2wks) **with A** (30mg 3x/w, 4wks) up to 4 cycles. A response rate of 47 and 78% as observed in the F-refractory and 17p relapsed patients of the GCLLSG CLL2O trial.[42] In the NCRI CLL 206 trial an OR of 77%, a CR of 14% with a median PFS of 6.5 mo and an OS of 19.5 mo was reported in previously treated patients.[28]

Ofatumumab, a human anti-CD20 monoclonal antibody, binds a distinct epitope on the CD20 molecule, induces more effective complement-dependent cytotoxicity even in CLL cells with low CD20 expression and shows a slower off-rate compared to

rituximab. Ofatumumab has been licensed for the treatment of fludarabine and alemtuzumab (FA)-refractory CLL. An international, multicenter trial recruited patients with FA-refractory and F-refractory CLL with bulky lymphadenopathies (BF) (>5 cm) for treatment with ofatumumab. The final results revealed an OR of 51%, a duration of response of 5,7 mo and an OS of 14,2 mo for the FA-refractory group and an OR of 44%, a duration of response of 6 mo and OS of 17,4 mo for the BF-refractory group. Responses seem equal for patients previously treated with rituximab versus rituximab naïve patients.[43] Ofatumumab with high-dose methylprednisolone seems also an effective salvage treatment (OR 4/8) for heavily pretreated, unfit or refractory CLL patients.[44]

Allogeneic SCT should be considered as a reasonable therapeutic option for CLL patients with progressive disease and an acquired 17p deletion or refractory to fludarabine, alemtuzumab or CIT and early relapse after CIT (<24 mo).[29] Reduced intensity conditioning should be preferred because non-relapse mortality is lower compared to conventional myeloablative allo-SCT. This is a feasible procedure up to seventy years of age with a better outcome if the disease is chemo-sensitive, bulky adenopathies are absent and the patient is not exposed to alemtuzumab in the last twelve months.

Maintenance or consolidation treatment

It has been shown in several trials that patients with eradication of MRD have a longer PFS and a better OS than MRD positive patients. However, a significant proportion of patients will remain MRD-positive even after the most active CIT.[45] Several studies confirmed the potential of alemtuzumab and rituximab as consolidation treatment to improve suboptimal responses, as converting patients from PR to CR or convert patients from MRD positive to MRD negative. However, it is unclear if the benefits of eradicating MRD may outweight the risk of an extended period of immune suppression.[46] Lenalidomide has shown to modulate the CLL microenvironment and the immune response to CLL cells and is currently evaluated as a maintenance drug.[47]

For the time being, achievement of MRD as a goal of therapy or MRD-guided intervention cannot be advised outside of clinical trials.

Future treatment approaches

Several ongoing clinical trials are exploring new agents for the treatment of CLL.

These include monoclonal antibodies (novel anti-CD20 (ofatumumab, obinutuzumab (GA101), anti-CD40 (lucatumumab), anti-CD37, anti-CD19 antibodies,…), signal transduction inhibitors (GS-1101 (CAL-101) a specific inhibitor of the delta isoform of phosphatidylinositol-3-kinase, ibrutinib (PCI-32765) an inhibitor of bruton tyrosine kinase, fostamatinib a Syk-inhibitor, inhibitors of mTor, tyrosine kinase inhibitors (imatinib, dasatinib)…), modulators of the microenvironment (lenalidomide, CXCR4 antagonists), cycline dependent kinase inhibitors (dinaciclib), apoptosis inducing agents (BH3 mimetics (ABT-263),…), hypomethylating agents, histone deacytelase inhibitors and chimeric antigen receptor-engineered T cells. Among these new approaches, the signal transduction inhibitors GS-1101 and ibrutinib have shown remarkable activity in very advanced patients independent of genetic aberrations.

Richter transformation

Transformation of CLL to large cell lymphoma or Hodgkin's disease is known as Richter's syndrome (RS). The development of RS may represent either a clonal progression of the CLL or a de novo development of an independent lymphoid malignancy. RS is not a rare event in the natural history of CLL since the cumulative incidence at ten years exceeds 10%.[48] R-based chemotherapy (R-CHOP, oxaliplatin, fludarabine, cytarabine, rituximab (OFAR), …) is proposed for RS, histologically classified as DLBCL.[48] As the median survival time with CIT alone is less than twelve months, young and fit patients, responding to induction CIT are candidates for allogeneic SCT according to the EBMT guidelines.[29] The outcome of Hodgkin variant of RS is slightly better. These patients must be treated with a Hodgkin specific chemotherapy regimen. Rituximab is a potential additional therapeutic option for patients whose Reed-Sternberg cells express the CD20 antigen.[49]

Autoimmune complications

The proportion of CLL patients who present with autoimmune cytopenia at some point during the course of the disease varies between 4 and 10%. Autoimmune haemolytic anemia (AIHA) is the most common complication followed by immune thrombo-

cytopenia (ITP). Pure red cell aplasia and autoimmune neutropenia (AIN) are rare. Corticosteroids remain the treatment of choice. Alternative immunosuppression (cyclosporine, mycophenolate mofetil, azathioprine) should be considered in patients failing to respond to corticosteroids, relapse soon after corticosteroid withdrawal or require a high maintenance dose. Monoclonal antibodies (rituximab and alemtuzumab) alone are in combination with immunosuppressive agents have been used successfully. Splenectomy remains an effective treatment particularly for ITP. Case reports have shown that thrombopoietin receptor agonists are efficacious also in CLL mediated ITP. AIN can be treated with G-CSF.[50]
Whereas patients with a non-fludarabine related AIHA or a positive Coombs can be safely treated with purine analogue combinations, rechallenge with purine analogues after a fludarabine-related AIHA should be avoided.[51]

Conclusion

The BHS lymphoproliferative group recommends:

- **No treatment for patients without active and/or advanced disease**, regardless of prognostic factors *(Figure 1)*
- **Front-line treatment** for patients with advanced and/or active disease *(Figure 1)*
  - **FCR** for **fit** patients as this treatment can prolong overall survival *(grade of evidence: level Ib, grade of recommendation: A)*
  - **BR** for patients **unfit for FCR** (renal function impairment, comorbidities, frequent infections, active hemolysis, …) as this treatment can prolong PFS substantially *(grade of evidence: level IIa, grade of recommendation: B)*
  - **Chlorambucil** for **older patients with a geriatric profile or patients with major comorbidities or a reduced PS** to control symptoms and keep toxicities at a minimum *(grade of evidence: level Ia, grade of recommendation: A)*
  - Consider **RIC allogeneic SCT** for patients with **a 17p deletion or *TP53* mutation** after induction with an alemtuzumab-based regimen or FCR as these regimens induce comparable response rates and response durations *(grade of evidence: level IV, grade of recommendation: C)*
- **Second or subsequent treatment** for patients with recurrent or refractory advanced and/or active disease
  - **Previous treatment can be repeated if the duration of response has lasted >1 year following chemotherapy or >2 years following CIT** *(grade of evidence: level IV, grade of recommendation: C) (Figure 2)*
  - Consider **RIC allogeneic SCT** or **consolidation treatment in a clinical trial** if the patient is not eligible for transplant for the following patients after a reinduction treatment as their median OS is <2 years *(grade of evidence: level IV, grade of recommendation: C)*:
    - an **alemtuzumab-based regimen** for patients with a **17p deletion or** *TP53* **mutation** *(grade of evidence: level IIa, grade of recommendation: B)*

Key messages for clinical practice

1. No treatment is necessary for patients without active and/or advanced disease, regardless of prognostic factors
2. FCR for fit patients, BR for patients unfit for FCR and chlorambucil for older patients with a geriatric profile or patients with major comorbidities or a reduced PS is recommended as front-line strategy
3. The choice of treatment for patients with recurrent advanced and/or active disease depends on the duration of response to the previous treatment and on the type of treatment refractoriness
4. RIC allogeneic SCT should be considered as a reasonable therapeutic option according the EBMT recommendations
5. Patients must be encouraged to enter clinical trials exploring new agents

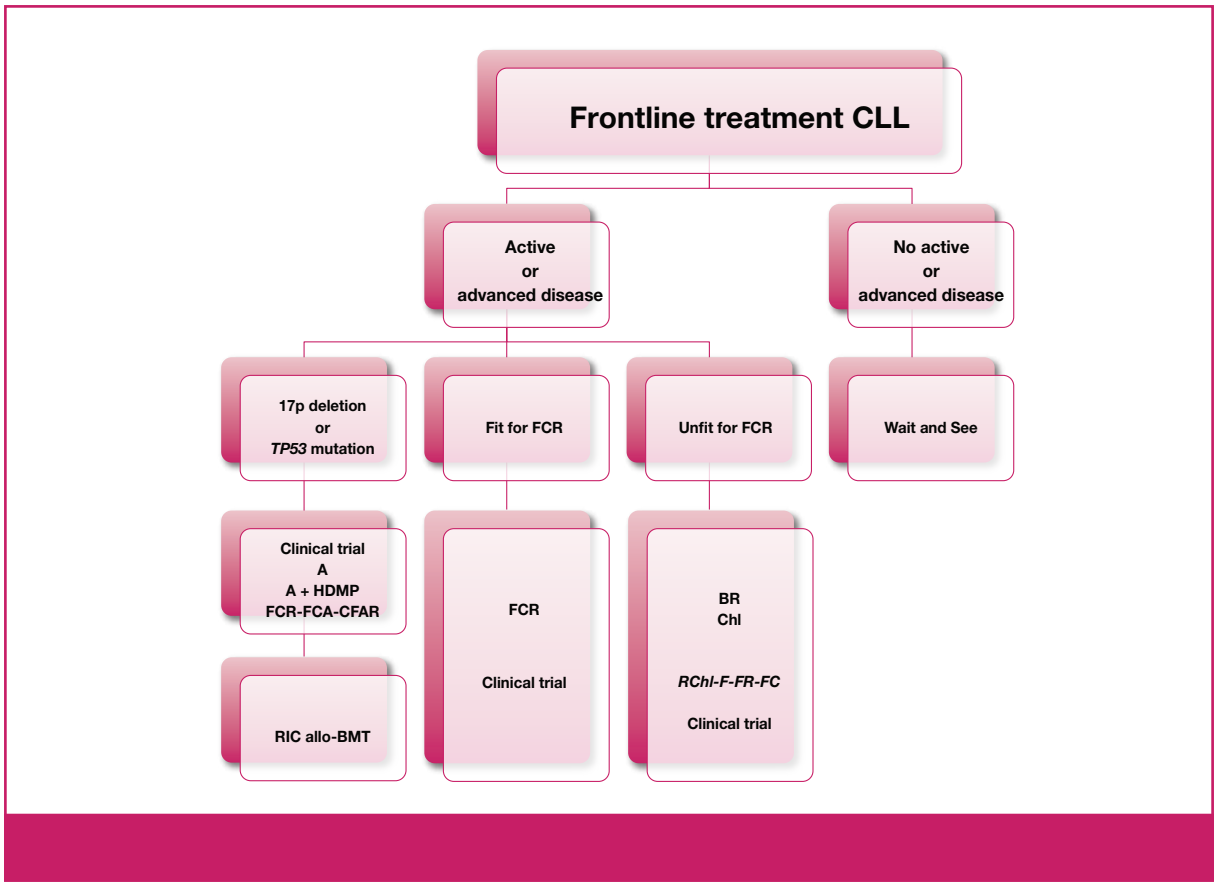

Figure 1. Algoritm for the frontline treatment of CLL. (A: Alemtuzumab; HDMP: high dose methylprednisolone; FCR: fludarabine, cyclophosphamide, rituximab; FCA: fludarabine, cyclophosphamide, alemtuzumab; CFAR: cyclophosphamide, fludarabine, alemtuzumab, rituximab; BR: bendamustine, rituximab; Chl: chlormabucil, F: fludarabine; FR: fludarabine, rituximab; FC: fludarabine, cyclophosphamide).

- an **alemtuzumab-based regimen** for **fludarabine refractory** patients *(grade of evidence: level IIa, grade of recommendation: B)*
- **ofatumumab** for **fludarabine and alemtuzumab refractory** patients *(grade of evidence: level IIb, grade of recommendation: B)*
- treatment with the **previous CIT** (if CR/nCR) or an **alternative CIT** for patients with **relapse < 2 years after CIT** *(grade of evidence: level IV, grade of recommendation: C)*

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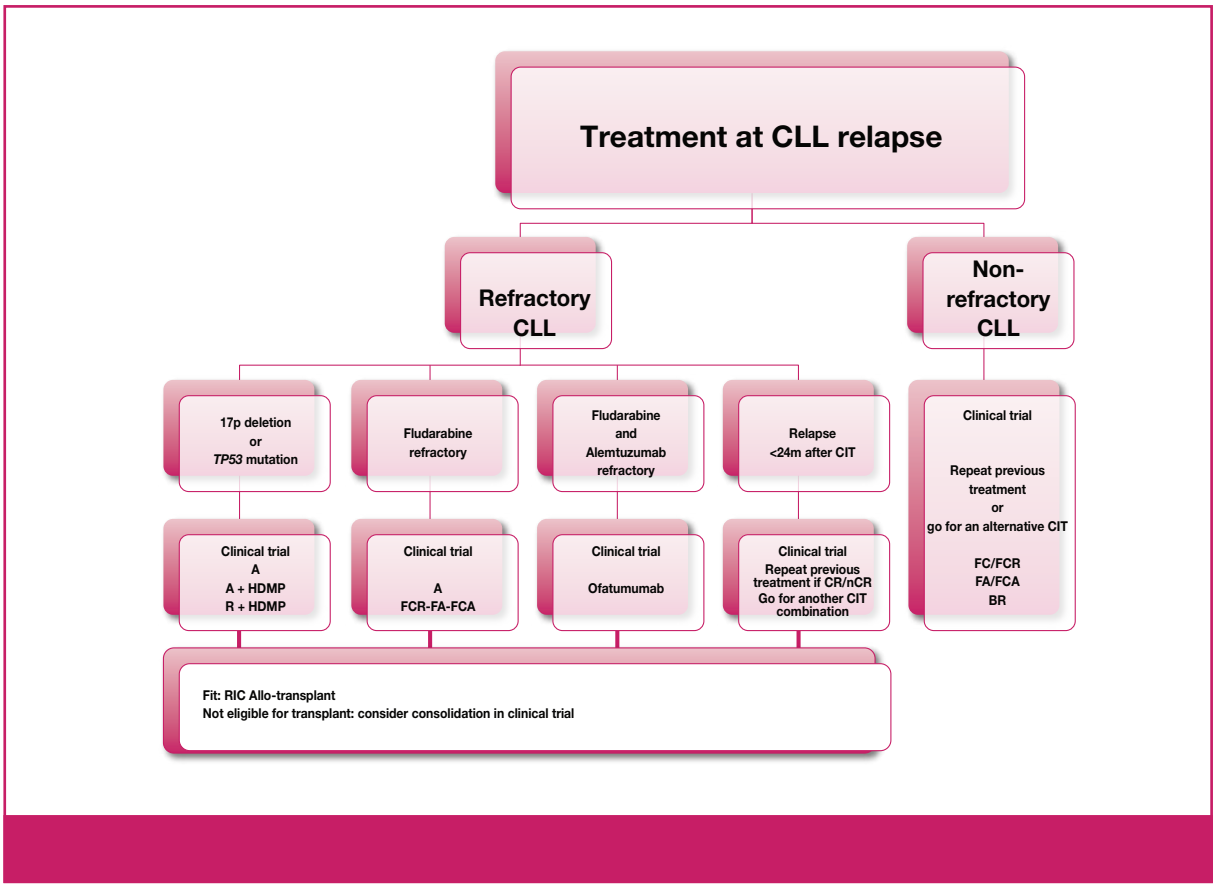

Figure 2. Algoritm for the treatment of relapsing and refractory CLL. (A: Alemtuzumab; R: rituximab; HDMP: high dose methylprednisolone; FCR: fludarabine, cyclophosphamide, rituximab; FA: fludarabine, alemtuzumab; FCA: fludarabine, cyclophosphamide, alemtuzumab; rituximab; BR: bendamustine, CIT: chemoimmunotherapy).

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