EUROPEAN HEMATOLOGY ASSOCIATION

Chronic lymphocytic leukemia - Section 3

Prioritizing therapies in chronic lymphocytic leukemia

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Take-home messages

- For CLL patients we have to prioritize treatment options based on clinical and novel molecular markers.
- Chemoimmunotherapy remains the standard-of-care for the majority of CLL patients in the frontline setting.
- Novels drugs like ibrutinib, idelalisib and venetoclax are nowadays treatment standards for CLL patients with relapsed/refractory disease.

In the last few years we have faced major breakthroughs in the understanding of the molecular pathways and mechanisms in malignant B cells that resulted in the development and partially also approval of new classes of drugs in chronic lymphocytic leukemia (CLL). Therefore, it is important to prioritize treatment options available based on clinical and molecular characteristics of the individual patient.

First, we have to be aware that the majority of patients still benefits from a watchful waiting in early stages of the disease. If the indication for treatment is given, we have to select those patients with an ultra-high risk profile, independent of age and fitness: patients with a 17p deletion and/or a TP53 mutation should be offered nowadays treatment with the BTK inhibitor ibrutinib.[1] If there is a contraindication for the use of ibrutinib, the PI3K inhibitor idelalisib (in combination with rituximab) could be applied.[2] As an alternative, the BCL2 inhibitor venetoclax has recently been approved for patients being unsuitable for the use of a B-cell receptor inhibitor (BCRi).[3]

The majority of patients will not show an aberration of the TP53 gene, neither a deletion nor a mutation. Here we have to adapt the therapy based on classic criteria, i.e. age and fitness. It becomes apparent that more and more the IGHV status might help to choose for the most adequate treatment for specific subgroups. Nowadays, for fit patients (based on CIRS score) that are not older than 65 years, a combination treatment based on fludarabine, cyclophosphamide and rituximab (FCR) would still be the standard-of-care. Especially patients with a mutated IGHV and no further high risk features besides 17p-/TP53mut will statistically have a long-term progression-free survival, based on several independent trials by different study groups.[4,5] Nevertheless, we have to await the results of the FLAIR trial by the UK CLL Study Group that will challenge the FCR standard in comparison to a combination of ibrutinib and rituximab. If a patient has been defined to be fit, but is older than 65 years we would rather recommend a treatment based on the doublet of bendamustine plus rituximab (BR). Here the CLL10 trial of the GCLLSG has shown that BR resulted for fit elderly patients in similar efficacy compared to FCR, but significantly less toxicity.[6] The prioritization of therapies in the elderly non-fit patients without ultra-high risk features is more difficult because we do have several options that have not been compared to each other within controlled clinical trials. Based on the COMPLEMENT-1 trial the combination of chlorambucil plus ofatumumab has been shown to be superior to a classic monotherapy with chlorambucil.[7] Furthermore, the CLL11 trial conducted by the GCLLSG has proven that chlorambucil plus obinutuzumab is the treatment of choice in less fit elderly patients, this in comparison to a chlorambucil monotherapy and a doublet based on chlorambucil plus rituximab.[8] The MABLE trial has recently been presented with preliminary data showing a superiority of BR compared to chlorambucil plus rituximab.[9] Finally, ibrutinib has been approved in the frontline setting based on a phase III trial (RESONATE-2) that included patients above the age of 65. This trial demonstrated significant PFS and OS advantages for ibrutinib when being compared to chlorambucil

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(without anti-CD20 mAb).[10] Despite the limitation of the comparator arm, ibrutinib monotherapy received the EMA label for frontline treatment in CLL, irrespective of age and fitness. Nevertheless, the hematology community is awaiting the data of the ILLUMINATE trial that performs a head-to-head comparison of ibrutinib to chlorambucil, both drugs being used in combination with obinutuzumab. Since subgroup analysis have shown that ibrutinib has the same efficacy independent from the IGHV status, ibrutinib frontline treatment could be prioritized for elderly non-fit patients with an unmutated IGHV in countries where ibrutinib is available in this setting.

While the options in the first-line treatment setting seem to be well defined (see Figure 1), the therapeutic armamentarium in the relapsed setting (see Figure 2) is less clear due to the fact that only few randomized trials have been performed in the past years. There is a consensus that chemoimmunotherapy can be repeated in patients that have been in remission for at least three years after frontline therapy, however BCR inhibitors could be used alternatively, notably after testing again for unfavorable genetic markers such as TP53 aberrations. While the option of reinduction with classic chemoimmuntherapy in case of late relapses might be real in a younger and fit patient, it is becoming more and more theoretical in elderly patients since toxicity of chemotherapy might become a burden with increasing age. Especially in elderly late relapsing patient, but also in cases of early relapse or even for patients with refractory disease after frontline chemoimmunotherapy, we should go for one of the new agents like ibrutinib or idelalisib (the latter in combination with rituximab). Ibrutinib has been randomized to ofatumumab in the RESONATE trial and has demonstrated a PFS and OS advantage.[11] Idelalisib (plus rituximab) was shown to be superior to a rituximab monotherapy comparator arm.[12] Both drugs have been approved by the EMA in the relapsed setting, after at

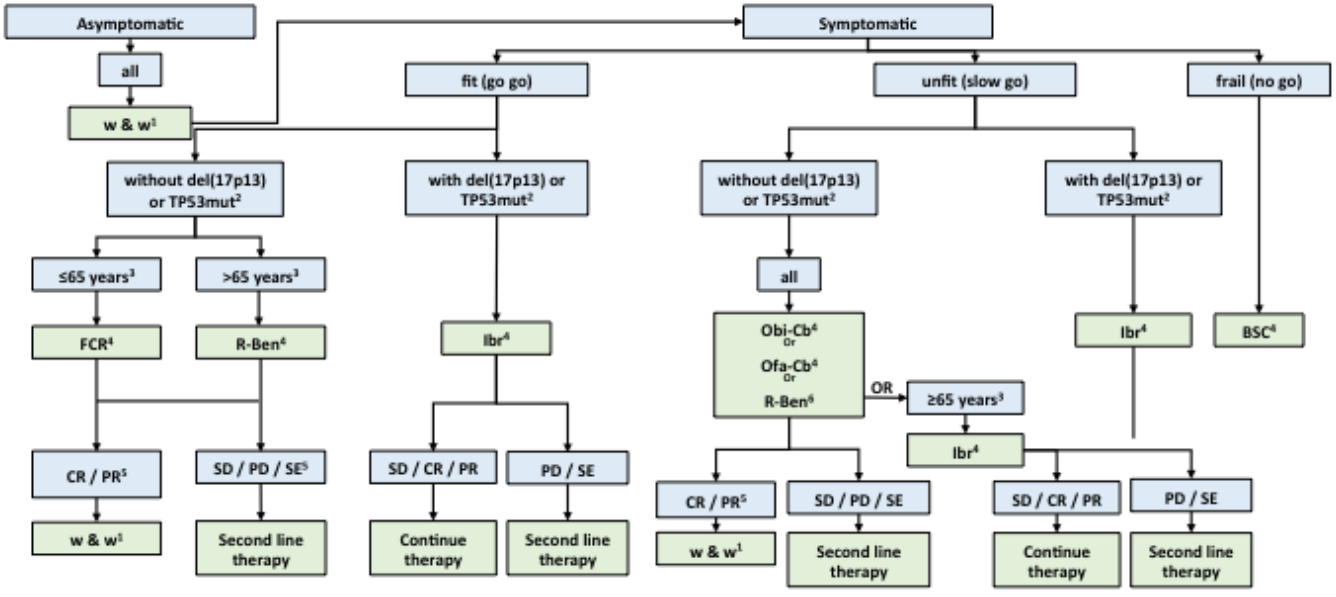

Figure 1. 1st line treatment recommendations for CLL

Adapted from Wendtner CM, et al. Onkopedia January 2017. Available at: https://www.onkopedia-guidelines.info/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll
[1]w & w – watch and wait; [2]based on FISH (17p-) and Sanger sequencing (TP53mut); [3]Based on the inclusion criteria of the underlying studies; Therapy based on comorbidity and less on age [4]Therapy: Ben - bendamustine, BSC - Best Supportive Care, C - cyclophosphamide, Cb - chlorambucil, F - fludarabine, Ibr - Ibrutinib, Obi - obinutuzumab, Ofa - ofatumumab, P - prednisone, R - rituximab; [5]CR – complete remission, PD – progressive disease, PR - partial remission, SD - stable disease, SE – Side effects. [6]Dose reduction of bendamustine to 70 mg/m² (day 1 +2) in patients in unfit state (slow go).

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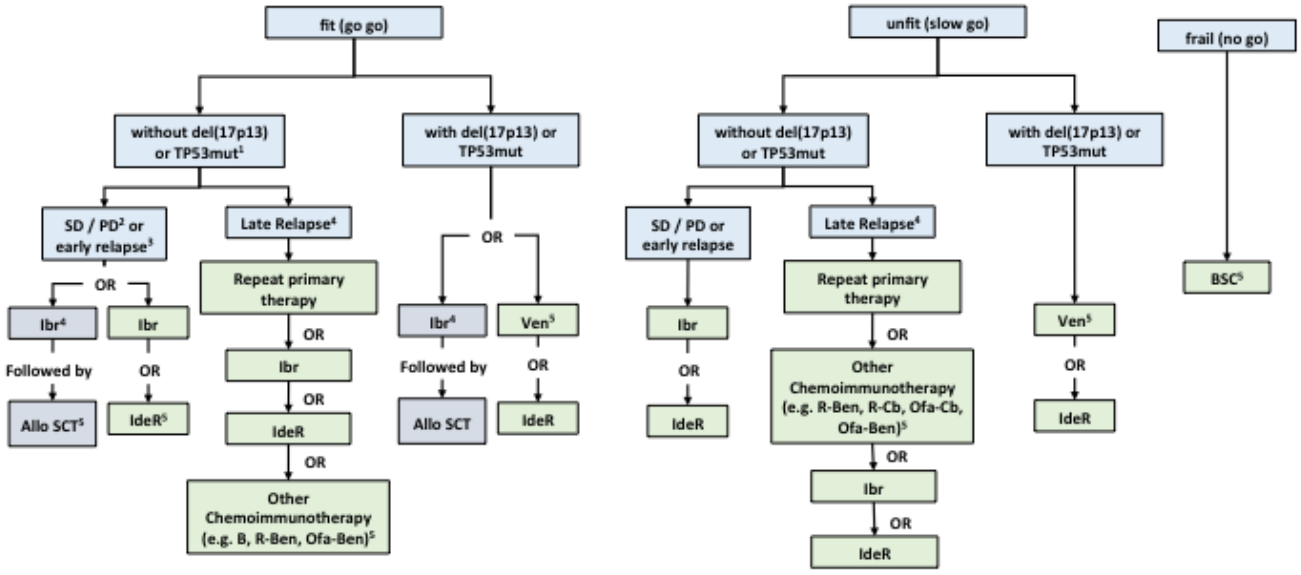

Figure 2. 2nd line treatment recommendations for CLL

Adapted from Wendtner CM, et al. Onkopedia January 2017. Available at: https://www.onkopedia-guidelines.info/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll
[1,2]based on FISH (17p-) and Sanger sequencing (TP53mut); [2]PD – Progressive disease, SD – Stable disease. [3]Early relapse – within 2-3 years; [4]Late relapse – later 2-3 years; [5]Therapy: allo SCT – allogenic stem cell transplant, Ben - Bendamustine, BSC – Best Supportive Care, Cb – Chlorambucil, Ibr – Ibrutinib, Ide – Idelalisib, Obi – Obinutuzumab, Ofa – Ofatumumab, P – Prednisone, R – Rituximab, Ven – Venetoclax.

least one line of prior therapy. For patients with a ultra-high risk aberration (17p-, TP53mut) in the relapsed/refractory setting both drugs are the treatment of choice. If a patient with a 17p-/TP53mut feature has seen one of these BCR inhibitors before, one option would be to switch from a BTK inhibitor to a PI3K inhibitor or vice versa. Presumably a better option, although never proven in a randomized fashion, would be to offer the BCL2 inhibitor venetoclax in case of a BCRi failure.[13] Venetoclax is also approved for patients with failure to chemoimmunotherapy and BCRi, irrespective of the TP53 status. Current and future trials will analyze whether we can limit the exposure to treatment, also including new drugs that have otherwise to be used indefinitely, by combining different drug classes with each other in order to improve the quality of life for our patients without taking the risk of an uncontrolled disease.

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In case of failure of a BCR inhibitor, the BCL2 inhibitor venetoclax is an effective treatment choice.