Chronic lymphocytic leukaemia—what is new and notable in 2021, with a special focus on COVID-19

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Summary In the last few years, treatment of patients exhibiting chronic lymphocytic leukaemia has changed extensively due to advances in the development of targeted therapies. The role of immunochemotherapy has been for the most part replaced and the guidelines have been modified accordingly. Herein, we give an overview on updated onkopedia guidelines, studded with updates of the landmark studies of the latest American Society of Hematology (ASH) meeting. In addition, since still crucial, recommendations concerning coronavirus disease 2019 (COVID-19) in chronic lymphocytic leukaemia patients will be covered.

Keywords Chronic lymphocytic leukemia · Targeted therapy · Coronavirus disease 2019 · Bruton tyrosin kinase · Bcl2-inhibitor

The approval of various new, targeted therapeutics in chronic lymphocytic leukaemia (CLL) has led to a paradigm shift in the treatment of this malignant disease. The gold standard hitherto, immunochemotherapy, has been almost replaced by new substances, targeting directly the pathway of malignant B-cell development. The persuasive results of various phase 3 studies have been already incorporated in the new onkopedia guidelines and led to an omission of chemotherapy with all its known and formidable side effects [1].

Independent of all changes, the diagnosis of CLL remains a domain of flow cytometry, which can also be used in minimal residual disease surveillance. However, the presence of an unmutated immunoglobulin heavy-chain variable (IGHV) region status and/or a complex karyotype, beside the already established adverse risk feature of a TP53 mutation or a deletion 17p, now defines the CLL patient as high risk and changes the therapeutic algorithm. Complex karyotype is defined as the existence of five or more chromosomal aberrations or at least three aberrations together with a TP53 mutation. Therefore, fluorescence in situ hybridization (FISH), sequencing of TP 53, chromosome banding analysis and IGHV mutation analysis is obligatory before initiation of therapy.

The importance of molecular diagnosis is reflected by a change of risk stratification. Former important parameters like age and fitness status have been abandoned in favour of genetic abnormalities, which now define patient subgroups.

The new targeted therapies ascertain almost all lines of therapy. Patients in need of first-line therapy and without risk factors (as determined above) may receive an inhibitor of the Bruton tyrosine kinase (BTKi) with or without an anti-CD20 antibody. All currently approved BTKi-based therapies are administered indefinitely, until disease progression or intolerance. The superiority of ibrutinib over chemoimmunotherapy (rituximab plus bendamustine, rituximab plus fludarabine plus cyclophosphamide) has been demonstrated in fit and unfit patients [2, 3]. For acalabrutinib, also approved for the treatment of newly diagnosed (and relapsed) CLL patients, an improved progression-free survival (PFS) has been shown, compared to chlorambucil and obinutuzumab [4]. If comorbidities exclude patients from the use of BTKis or the desire for a limited therapy predomi-

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nates, the BCL2-inhibitor venetoclax, in combination with the anti-CD20 antibody obinutuzumab is an equivalent option. According to the CLL14 trial, after a 5-week ramp-up phase for venetoclax, the two substances were administered for 6 months (obinutuzumab) or one year (venetoclax) respectively, and stopped thereafter [5]. Results were clearly superior to those of the combination of rituximab and chlorambucil. For a small subgroup of young and fit patients, especially those harbouring a mutated IGHV status, chemoimmunotherapy with rituximab, fludarabine and cyclophosphamide (FCR) may remain a treatment option, based on the results of the CLL8 study, showing a plateau in PFS for patients who are IGHV mutated, after receiving FCR [6]. Older patients may also benefit from the treatment with obinutuzumab and chlorambucil or bendamustine and rituximab, but as for FCR before, only a small subset of patients with an mutated IGHV status will qualify for these treatment options [7, 8]. Patients who present with high-risk features, namely TP53 mutation, deletion 17p, complex karyotype or unmutated IGHV status, should exclusively receive targeted therapies, exemplified by the dismal results with immunochemotherapy in this subgroup of CLL patients. A recent update showed promising results concerning the long-term efficacy of ibrutinib in this high-risk patient group [9].

In second and further lines of therapies, again high-risk features as well as preceding therapies decide about sequencing of subsequent therapies. In high-risk patients, BTKis or venetoclax should be preferably used, and especially younger patients failing a BTKi and venetoclax (or with dismal response to preceding therapies) should not be excluded from allogeneic stem cell transplantation, which remains still the only treatment with curative intent. Patients, who have undergone immunochemotherapy as first-line therapy and showed long durations of response, may benefit from a repetition of front-line therapy. When BTKis have been used in the front-line setting and patients present with progression under therapy, a switch to venetoclax in combination with rituximab, the so-called MURANO scheme is recommended [10]. Therein, the superiority in PFS and overall survival (OS) of a 24 months limited therapy with venetoclax and rituximab over bendamustine and rituximab has been demonstrated. A 5-year update from the latest ASH meeting confirmed these results with a significant proportion of patients remaining with undetectable MRD at this follow-up. Nevertheless, this group showed an increased permanent hazard for loss of MRD conversion and clinical relapse [11].

Second line therapy after first-line venetoclax usage depends on the duration of response. After at least 3 years of response [12], a repetition can be considered. Otherwise, a change to a BTKi, with or without an anti-CD20 of 1 L antibody can be suitable [13–15].

With the usage of targeted therapies, a change in required resources was necessary. While immunochemotherapies needed hospital treatment for at least a few days, a majority of the now used schemes can be applied in the outpatient setting. An exception constitutes the ramp-up phase of venetoclax, which in high-risk situations should be performed inpatient to avoid a possible clinical tumour lysis syndrome. In addition, a quantum of “new side effects” associated with novel targeted treatments and their handling have been introduced to haematologists. Beside the known, haematological adverse effects, for instance cardiac events under ibrutinib represent a new category of side effect management.

Naturally, coronavirus disease 2019 (COVID-19) infections also apply to CLL patients and various questions concerning testing, treatment and vaccination appeared. In short time, scientific efforts like never before are able to answer a lot of these questions and an expert consensus, regularly updated, gives input in distinct problems [16].

While CLL patients are prone to various bacterial and viral infections, due to their immunodeficiency, there is no evidence up to now that they are disproportionately more often affected by a COVID-19 infection than other cancer patients. Nevertheless, the mortality of CLL patients, suffering from severe COVID-19 course of infection, is high, independent of whether they are under therapy or follow a “watch and wait” strategy. A recent meta-analysis reported a mortality rate of 31% and similar to the normal population, mortality rate increases with age of the patients [17].

There is also a clear statement concerning the initiation of treatment in patients requiring therapy, whenever necessary according to iwCLL criteria, no treatment delay should be pursued. In the case of different therapy options, the one with the least clinic visits with the least immunosuppressive potential should be favoured. The role of anti-CD 20 antibodies, especially when combined with targeted therapies, is also controversial, given their high immunosuppressive properties [16].

Patients, already undergoing CLL specific therapy should not change treatment; whenever possible, the number of visits should be reduced and the use of anti-CD20 antibodies should be reconsidered.

If a patient undergoing CLL-specific therapy is tested positive for COVID-19, no change is recommended for patients with mild symptoms in the outpatient setting. In cases with severe symptoms, the attending physician must gauge the decision between necessity of therapy because of aggressiveness of the disease and possible complications of a COVID infection. In these cases, an individual approach for each patient must be followed. Up to now, there exist no reliable data supporting a class-specific approach. However, some data support a possible protective effect for BTKis in (severe) COVID-19 infections and therefore, the expert panel supports the continuation

of BTKi therapy [18]. Venetoclax due to a pronounced lymphopenia should be held back as advised by the majority of experts. A strong consensus exists about discontinuation/and or delaying of anti-CD20 antibodies. It has to be noted that radiologic COVID-19 findings can be mimicked by opportunistic infections.

There also exists a general recommendation for anti-COVID vaccination, based on an individual case-by-case decision. In the landmark phase III randomized control trials, immunocompromised patients have been largely excluded although this high-risk group should have been prioritized [19]. The immune response towards the vaccination may vary, given the heterogeneity of the disease. A case report, analysing the sera of 21 vaccinated patients with underlying CLL, revealed a development of IgG antibodies in 14 (67%) patients. The nonresponders were both treatment-naïve or patients with current therapy [20]. Recently, Herishanu et al. confirmed the recommendation, demonstrating adequate antibody-mediated response in CLL patients who obtained clinical remission after treatment but only dismal immune response in patients under treatment at the time of vaccination [21]. Both ibrutinib- and venetoclax-treated patients showed low response rates. Expectedly, none of the patients exposed to anti-CD20 antibodies < 12 months prior to vaccination responded.

The eminent reams of new substances now available in treatment of CLL pose new challenges for the attending haematologist. Additionally the corona pandemic does not simplify therapeutic strategies. Nevertheless, the perspectives for CLL patients have never been so optimistic before and may improve further with upcoming studies of combination therapies.

Take home message

Targeted therapies have almost replaced the immuno-chemotherapies in the treatment of chronic lymphocytic leukaemia. New challenges not only due to COVID-19 (coronavirus disease 2019) are demanding for the attending haematologist.

Conflict of interest K.T. Prochazka and P. Neumeister declare that they have no competing interests.

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