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Initial therapy of chronic lymphocytic leukemia

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ABSTRACT

Only chronic lymphocytic leukemia (CLL) patients with active or symptomatic disease or with advanced Binet or Rai stages require therapy. Prognostic risk factor profile and comorbidity burden are most relevant for the choice of treatment. For physically fit patients, chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab remains the current standard therapy. For unfit patients, treatment with an anti-CD20 antibody (obinutuzumab or rituximab or ofatumumab) plus milder chemotherapy (chlorambucil) may be applied. Patients with a del(17p) or *TP53* mutation should be treated with the kinase inhibitors ibrutinib or a combination of idelalisib and rituximab. Clinical trials over the next several years will determine, whether kinase inhibitors, other small molecules, immunotherapeutics, or combinations thereof will further improve outcomes for patients with CLL.

1. Introduction

For patients with chronic lymphocytic leukemia (CLL) treatment possibilities and efficacy of various treatment regimens has changed dramatically during the past decades. For a long time, treatment of CLL was a very palliative approach starting with the introduction of the alkylating chlorambucil in 1956 [1]. Treatment with chlorambucil alone or in combination with corticosteroids showed the first remarkable remissions [2,3]. In the 1980s combination therapies with cyclophosphamide, doxorubicine, vincristine, and prednisolone (CHOP) or similar regimen, eg, COP, were compared to chlorambucil within randomized studies but were not able to show a clear benefit due to a higher toxicity rate [4–6]. Hence, chlorambucil was the treatment of choice for decades until a new agent group of chemotherapeutic agents, the purine analogues (including the substances fludarabine, cladribine, pentostatin), was introduced [7,8]. Fludarabine monotherapy resulted in a significantly better response rates as well as longer progression-free survival (PFS) in comparison to CHOP [9]. Similar results were obtained with fludarabine or cladribine in comparison to chlorambucil [10,11]. The combination of purine analogues with cyclophosphamide yielded significantly higher rate of complete remission and furthermore an additional prolongation of relapse-free time [12–15]. With the addition of rituximab to these regimen or to single-agent chemotherapeutic agents a treatment standard in previously untreated CLL was defined, the CD20 antibody-based chemoimmunotherapy regimen. The new targeted treatment substances, approved mainly for the relapsed and refractory situation and currently investigated in several studies for upfront treatment, will change frontline therapy of CLL in the near future. The article summarizes current treatment options focusing on chemoimmunotherapy as well as chemotherapy-free regimens.

2. Indication for treatment initiation

In general practice, newly diagnosed patients with asymptomatic early stage disease (Rai 0, Binet A) should be monitored unless they develop symptoms of active and/or progressive disease. Previous studies have shown that early treatment with alkylating agents does not translate into a survival advantage in patients with early-stage CLL [16,17]. Treatment should be initiated in patients with advanced stage disease (Rai III and IV or Binet C). Patients with intermediate stage (Rai I and II or Binet B) can be monitored until they have symptoms of progression and/or symptomatic disease. According to the International Workshop on CLL (IWCLL) guidelines the following conditions define active disease: significant B-symptoms, cytopenias not caused by autoimmune phenomena, autoimmune anemia and/or thrombocytopenia poorly responsive to conventional therapy, symptoms or complications from lymphadenopathy, splenomegaly, or hepatomegaly, as well as lymphocyte doubling time of less than six months (only in

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