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Refractory chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder characterized by the progressive accumulation of monoclonal peripheral B cells in bone marrow, peripheral blood and lymphoid tissues. Median survival is about 10 years but it ranges from less than 3 years to a normal life expectancy. Previously, treatment of patients with CLL was based on the use of alkylating agents such as chlorambucil, with resulted in a complete response rate minor than 10%, with a palliation of symptoms and no impact on survival. The introduction of purine analogs and rituximab in first line have improved the complete remission rate, the overall response rate and OS.[1]

Although the high rate of remission now achieved with purine analogs and monoclonal antibodies the risk of relapse is still consistent and most of patients with CLL relapses after primary treatment possibly because of microscopically persistence of the disease. It is important to distinguish between refractory and relapsing disease. Refractory CLL it could be defined as the lack of response or progression within the first year of treatment with purine-analogues containing regimens or disease progression within 2 years after autolgous stem-cell transplantation.[3] Whereas treatment of patients with relapsing disease can be investigated as in newly diagnosed patients, refractory disease requires immediate intervention. These patients are characterized by a very poor prognosis, with a median survival of 10-13 months. The anti-CD 52 monoclonal antibody alemtuzumab is an effective agent to treat patients with refractory disease. In the pivotal study of alemtuzumab in 93 patients with fludarabine refractory CLL, the overall response rate was 33%, with only 2 pts achieving CR. The median time to progression was 9,5 months, and there was an improvement in survival in responding patients at 32 months.[4] Alemtuzumab has a poor activity against bulky lymphadenopathy, but demonstrates efficacy in clearing the peripheral blood and bone marrow.

Rituximab alone is not effective in refractory CLL but it may be used in association with other drugs to enhance their effect. Lots of trials have tested rituximab in combination with other agents such as fludarabine, mitoxantrone, cyclophosphamide, and have shown that these regimens are active in CLL, including refractory case.[5,6,7] Wierda *et al.* reported treatment results in patients with either relapsing or refractory CLL using a combination of fludarabine, cyclophosphamide, and rituximab. Response rate among 33 patients refractory to fludarabine was 58% (6% CR, 9% nodular PR

[nPR], and 42% PR) compared with 77% (33%CR, 19% nPR, 24% PR) in 78 fludarabine-sensitive patients; time to progression, however, was quite short (median, 18 months; range, 3 to 49 months).[8]

Autologous transplantation in CLL led to a survival improvement only in chemosensitive patients: in fact there is a strong correlation between the outcome of autologous transplants and the status of the disease.[9]

Instead, allogeneic transplantation can induce durable responses also in patients with refractory disease.[10] Different studies have demonstrated the achiving of a plateau, with 40–60% of patients alive and disease free after transplantation.[11,12]

In conclusion, there is no standard therapy for refractory patients. The allogeneic BMT with reduced intensity conditioning regimens seems to be a possible strategy. Therefore the necessity to discuss clinical trials devoted to investigate biological features in this subset of patients and clinical outcome using allogeneic procedure.

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