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Ibrutinib, a Novel Agent in Relapsed or Refractory Chronic Lymphocytic Leukemia

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Refractory or relapsed chronic lymphocytic leukemia is still a hematologic malignancy with an unfavorable evolution after several lines of chemotherapy, even when associated with immunotherapy.

The additional presence of adverse prognostic factors such as17p deletion, 11 q deletion, unmutated IgVH genes, CD 38 and ZAP 70 expression further limits therapeutic possibilities.

Over the past two years numerous studies have focused on finding new therapeutic options useful in cases of relapsed or refractory chronic lymphocytic leukemia.

Ibrutinib is a new agent that has shown efficacy in treating these cases, the benefits of response and survival rate having been obtained using Ibrutinib as monotherapy, as well as in combination with immunotherapy or chemotherapy.

Ibrutinib irreversibly inhibits Bruton's tyrosine kinase, which is an important enzyme in the B cell receptor activation pathway for both normal and malignant B lymphocytes. Ibrutinib, administrated orally is involved in the inhibition of cytokines of the signaling pathways which mediate chemotaxis, of chemokines, also reduces the population of Ki67+cells and initiates apoptosis (1-3).

During the 10-15 months follow up period, a phase Ib/II trial concluded that treatment with ibrutinib leads to a lasting complete remission and increases survival without disease progression even in cases of Richter transformation or bulky disease (4-7).

Results are even more encouraging regarding previously untreated patients. In a group of 26 patients older than 65 years, disease progression free survival at 15 months was 96% (5,7).

Ibrutinib treatment was generally well tolerated, the major side effects related to administration were nausea, fatigue, diarrhea, rash and bruising. Grade 3-4 adverse reactions such as diarrhea, infections and hematological toxicity (anemia and / or thrombocytopenia), were reported with an average incidence of 10-13%. There was also an initial but transitory increase in absolute lymphocyte count, more pronounced in previously treated patients (4-6,8).

The partial results of the ongoing study indicate that the association of ibrutinib with bendamustine or ofatumumab tends to limit or prevent the appearance of lymphocytosis (8). Also Ibrutinib administration in combination

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with rituximab or bendamustine resulted in obtaining good quality remissions and a better quality of life (9,10).

Favorable results obtained with ibrutinib as monotherapy especially in previously untreated elderly patients, support the evaluation in phase III trials. Further Phase I studies related to the use of BTK class II (AVL-292) and specific inhibitors of the delta isoform of phosphatidylinositol-3 kinase (GS-1101), may bring hope and new perspectives in the therapy of chronic lymphocytic leukemia (8).

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