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A Review to Assess the Potential Benefits of Ibrutinib in Leukemia

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ABSTRACT

Ibrutinib is a novel drug that has been studied extensively for the treatment of various types of leukemia. It is a potent, irreversible inhibitor of burton's tyrosine kinase. Burton's tyrosine kinase is a crucial enzyme needed for the development of B cells. Since it holds such a promising pharmacological property, it is effective against leukemias. Ibrutinib gained accelerated approval from FDA for the treatment of chronic lymphocytic leukemia and mantle cell lymphoma. In 2015, the indication was extended to Waldenström macroglobulinemia. This novel anticancer drug has shown promising results in various types of leukemia. So this review article summarises the potential benefits as well as adverse effects associated with ibrutinib in the treatment of leukemia.

INTRODUCTION

Ibrutinib is an anticancer drug that was accepted by the FDA in 2013 for mantle cell lymphoma and chronic lymphocytic leukemia.

MECHANISM OF ACTION

The mechanism of action of ibrutinib is mainly associated with the B cell receptor pathway (BCR). In the BCR pathway activation, protein tyrosine kinases enzymes gets activated and subsequently, it leads to unwanted cell proliferation and cell differentiation. Ibritinib will form a covalent bond at the active site of btk 9burtons tyrosine kinase), which is one of the many protein kinases enzyme which are involved in the BCR pathway. This will inhibit its activity and subsequent initiation of transcription, leading to unregulated cell proliferation and cell differentiation.

CLINICAL STUDIES

Chronic lymphocytic leukemia and mantle cell lymphoma (CLL and MCL)

The phase 1 clinical studies by Advani et al showed prominent tolerance and significant therapeutic response in patients.[1]Durable response was maintained by the patients for a minimum period of 10 months. The drug showed highest rate of response in patients with mantle cell lymphoma and chronic lymphocytic leukemia. The response rate against mantle cell lymphoma is particularly noteworthy as bortezomib is the only drug that is used for the treatment of mantle cell lymphoma. Like other BCR antagonists, lymphocytic redistribution was observed in this study. Lymphocytic redistribution is a process which is associated with all the BCR antagonists in which there is a release of CLL cells from the stromal niches of the bone marrow or lymph nodes into the bloodstream where they eventually die. There was a transient increase in the levels of lymphocyte count in CLL patients. Another study by Byrd et al (phase 1b–2 multicenter study) showed high frequency of remission among patients with relapsed chronic lymphocytic leukemia.[2] 2 doses of ibrutinib was assessed in that particular study (420mg and 840mg) and both of them showed promising results. Another advantage of that particular study was that, Ibrutinib was effective even for chronic lymphocytic leukemic patients with cytogenetic lesions like 17p13.1 deletion. Promising results on phase 1 studies led to phase 2 studies. In the phase 2 clinical study by Wang et al showed that ibrutinib showed high durable activity against refractory mantle cell lymphoma. [3]A high response rate

of 68% was achieved in that particular study. Out of 68% response rate, 47% of patients having a partial response and 21% having a complete response. Another important study by O'Brien S et al, included elderly CLL patients who had no history of treatment.[4] 71% of the patients achieved objective response with an additional 13% achieving partial response with lymphocytosis. Even though this study shows the effectiveness of ibrutinib in high risk population, the number of patients who had genetic abnormalities like 17p13.1 deletion were relatively low.

Waldenström's macroglobulinemia (WM)

Waldenström's macroglobulinemia is a type of malignant disorder that is mainly occurring on the bone marrow and lymphatic tissues. It is mainly characterized by the presence of abnormal number of white blood cells and subsequent increase in number of IgM antibodies in the blood. The presence of these antibodies on the blood often leads to increase in the blood viscosity and subsequent symptoms of the disease. The treatment of WM is not standardized, and the choice of therapy is highly personalized and is based on the patient's age, symptoms, comorbidities or preferences. One of the most prominent study for WM was done by Treon et al. [5] In that particular phase 2 clinical study, the estimated progress free survival and overall survival was found to be 69% and 95%. The study was done on a total of 63 patients with response rate not differing based on age, sex, performance status, hemoglobin level, IgM level, bone marrow involvement, number of previous therapies or relapsed versus refractory disease. In fact, the total IgM level decreased from 3520 mg/dl to 880 mg/dl. In 2015, INNOVATE study reported overall and major response rates of 84% and 65%, with median IgM level (3830 mg/dl) decreasing by more than 50% on a population of 31 WM patients. [6]Both of these studies used ibrutinib 420 mg in order to produce these results. Ibrutinib is the only FDA-approved medication for patients with symptomatic WM. Ibrutinib has shown great efficacy at inducing deep and durable IgM responses, as well as improving hematologic parameters in patients with WM.

Diffuse large B cell lymphoma (DLBCL)

Diffuse large B cell lymphoma is a type of aggressive tumour that mostly occurs in older individuals and often affects B lymphocytes. Activated B cell-like DLBCL (ABC) and germinal centre B cell-like DLBCL (GCB) are the 2 distinct gene expression molecular subtypes has been associated with DLBCL. The activated B cell-like DLBCL (ABC) group

has a lower overall survival rate than the germinal centre B cell-like DLBCL (GCB) group. On a molecular level, these expression signatures can predict the outcomes of DLBCL. Since survival of ABC- DLBCL depends on the B cell receptor signalling, Ibrutinib is a rational drug of choice for the treatment. Wilson et al study which included a total of 68 patients with ABC DLBCL, ibrutinib showed clinically meaningful response. [7]The median progression free survival (PFS) rate was 60% in the ABC subgroup. Only one partial response was shown in GCB subtype. Thus, showing the effectiveness of ibrutinib against ABC- DLBCL.

Chronic graft vs host disease

Chronic graft vs host disease is a life threatening complication associated with allogenic hematopoetic stem cell transplantation. Though corticosteroids are considered as viable option as an initial therapy, treatment for patients who fail to respond to the initial therapy remains disputed. Since both B and T cells are associated with pathogenesis of graft vs host disease, ibrutinib can be considered as a viable option for patients who fails to respond to corticosteroids initial therapy. In a 2017 study by David et al, ibrutinib achieved 67% complete response on a heterogenous graft vs host cell population. More than 80% patients with multiple organ involvement showed response in more than 2 organs. [8]This particular study was marked by the discontinuation or reduction of corticosteroid use. Furthermore, changes in levels of tissue factors associated with fibrosis suggest a decreased propensity for tissue fibrosis and restoration of normal organ function. These findings, together with the demonstration of clinical response across multiple organs, support the hypothesis that ibrutinib is affecting the disease at a pathogenic level and not just treating symptoms of chronic graft vs host disease.

Marginal zone lymphoma (MZL)

Marginal zone lymphoma mainly occurs in three specific sites, namely, lymphoid follicles present in the spleen, mucosa-associated lymphoid tissues, and rarely on lymph nodes. Based on these sites, the world health organization (WHO) classified this disease into 3 specific subtypes. These subtypes include extranodal marginal zone lymphoma (EMZL), also called mucosa-associated lymphatic tissue (MALT) lymphoma; splenic MZL (SMZL); and nodal MZL (NMZL). Current investigations associated with ibrutinib has mainly been focused on refractory or relapsed marginal zone lymphoma. Phase II open-label international study was conducted using ibrutinib in patients with refractory or relapse MZL previously treated with

rituximab-based therapy. The study included 60 evaluable patients who were treated with single-agent ibrutinib (560 mg orally daily) administered until progression or unacceptable toxicity.[9] Objective response rate was 48% and progression free survival was 14.2 months. Complete response was responded in 2 patients (3%). Progression of disease was the main reason for treatment discontinuation, occurring in 32% of study participants. Though adverse events occurred in 44% of patients, the rates of treatment discontinuation and dose reduction due to AEs were relatively low at 17% and 10%, respectively.[14]Outcomes were also analyzed in MZL subtype. Median Progression free survival was 13.8 months for EMZL, 19.4 months for SMZL, and 8.3 months for NMZL. Estimated 18-month overall survival rate was 81%, and of the 8 patients who died during the study, 4 (7%) were attributable to progression of disease. Overall, the rate of disease control based on clinical benefit was 83%, and 78% of patients were shown to have reduced tumor burden. Clinical response to ibrutinib was seen in all subtypes.[9]

SAFETY PROFILE

Ibrutinib is proven to be well tolerated. In a safety analysis of four randomized controlled trials for chronic lymphocytic leukemia and mantle cell leukemia, ibrutinib showed favourable benefit to risk profile. [10] The most common AEs (≥ 20%) reported in all 4 of those randomized controlled trials were diarrhea, neutropenia, nausea, fatigue, pyrexia, anemia, and thrombocytopenia, all of which have been included in the ibrutinib prescribing information as common adverse reactions. One of the most common severe/life threatening adverse event was cytopenias. Cytopenias usually occurs within the first month of treatment with ibrutinib. But most patients with this haematological toxicity attained resolution (72%) in those trials. Another intriguing factor was incidence of atrial fibrillation, hypertension and hemorrhage. But all three of them were properly resolved. Similar type of optimal tolerance rate was reported by other studies as well. [11.12]Another intriguing study regarding the safety of ibrutinib was done by Steven E. Coutre et al in 2019. [13] This particular study assessed the long term safety of ibrutinib in CLL patients (in some cases, more than 5 years). This study reported the decline of neutropenia and infection during the long term use of ibrutinib. However, the presence of opportunistic infection was high in patients. So the study recommends prophylaxis treatment for opportunistic infections. Hemorrhage and hypertension was resolvable in most of the patients. However, the presence of atrial fibrillation was persistent throughout the study. This is contradictory to the previously

mentioned study which reported the presence of atrial fibrillation to be manageable. However other studies have already reported the presence of atrial fibrillation when using ibrutinib. [14] Overall, ibrutinib is a drug that was found to be safe for use on a long term with monitoring required for atrial fibrillation and haematological toxicities.

COMBINATION STUDIES

The promising results of ibrutinib as a monotherapy in CLL and MCL led to the testing of its efficacy when used with other drugs or regimens. Rituximab is a monoclonal antibody that has been used in combination with ibrutinib for the treatment of CLL as well as MCL. [15, 16] In the CLL study, forty high-risk CLL patients were included in a single-center Phase II study of ibrutinib in combination with rituximab. The patients received ibrutinib 420 mg per day orally in combination with rituximab 375 mg/m2 weekly during weeks 1–4 (cycle 1), followed by monthly rituximab until cycle 6, followed by continuation of ibrutinib until disease progression. The overall response rate was found to be 85% and the treatment was well tolerated, with mostly grade 1 to 2 adverse events, and only 13 cases of grade 3 or 4 toxicity, including neutropenia, fatigue, pneumonia, and bone pain. [15] In the MCL study, patients received continuous oral ibrutinib (560 mg) daily until progessive disease or unacceptable toxic effects. Rituximab 375 mg/m2 was given intravenously once per week for 4 weeks during cycle 1, then on day 1 of cycles 3–8, and thereafter once every other cycle up to 2 years.[16] MCL study achieved objective response, with 44% patients achieving a complete response, and 44% achieving a partial response. The only grade 3 adverse event in 10% of patients was atrial fibrillation, which was noted in six (12%) patients. Grade 4 diarrhoea and neutropenia occurred in one patient each.[16] However, only 50 patients were enrolled for the study. Another drug that has been studied in combination with ibrutinib is ofatumumab. The Phase Ib/II study of ibrutinib and ofatumumab included patients with relapsed/refractory CLL/small lymphocytic lymphoma who had received at least two prior therapies, including purine nucleoside analogs. Patients received ibrutinib 420 mg daily on a 28-day cycle until disease progression. Ofatumumab was administered at a dose of 300 mg on day 1 in cycle 2 and then as 2000 mg on days 8, 15, and 22 of cycle 2 and on days 1, 8, and 15 of cycle 3, and on day 1 in cycles 4–8. Twenty-seven patients were enrolled, including three patients with Richter's transformation, and who had already received at least six cycles at the time of evaluation. The overall response rate was 100% (one complete response) in the CLL/small lymphocytic lymphoma group, and two of three patients with Richter's

transformation achieved partial remission. The most common side effects were grade 1 to 2 in severity. Grade 3 to 4 side effects included anemia (11%), pneumonia (11%), and urinary tract infection (7%). [17] The treatment was well tolerated and highly active in patients with refractory CLL/small lymphocytic lymphoma. Similarly, ublituximab, another novel glycoengineered anti-CD20 monoclonal antibody has shown similar results for CLL. [18]

CONCLUSION

With the introduction of ibrutinib and its potential combination drug therapies, the treatment for leukemia will change dramatically in the upcoming years. Given its excellent safety and efficacy profile, ibrutinib should be an appropriate choice for chronic lymphocytic leukemia and mantle cell leukemia. It is also showing promising results in other types of leukemia but in order to get a more accurate understanding, its effect need to be explored in a larger population.

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