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Ibrutinib for chronic graft-versus-host disease after failure of systemic prior therapy *(free download)*

Ibrutinib is an irreversible inhibitor of Bruton tyrosine kinase (BTK) in B cells and interleukin-2–inducible T-cell kinase (ITK) in T-cells. It has previously demonstrated to be effective in the treatment of chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL).[1]

In this phase Ib/II, open-label, multicenter study Miklos et al., Stanford University School of Medicine, Stanford, US, evaluated the safety and efficacy of ibrutinib in 42 patients with Chronic graft-versus-host disease (cGvHD) who had failed ≥ 1 lines of systemic corticosteroid-based therapy.[1]

Treatment with ibrutinib in patients with cGVHD resulted in an improvement of symptoms among responders, a decrease in the median corticosteroid dose and a decrease in cGvHD-related inflammatory and fibrotic factors. The safety profile was acceptable and similar to what was observed in other indications. The results of this study led to the FDA approval of Ibrutinib for steroid-resistant cGvHD.[1]

1. Miklos D. et al., Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. Blood. 2017 Nov 23; 130(21): 2243–2250. DOI: 10.1182/blood-2017-07-793786

(free download)

Improved survival after acute graft-versus-host disease diagnosis in the modern era *(free download)*

Khoury H.J. et al., Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, US, examined data from the Center for International Blood and Marrow Transplant Research (CIBMTR) to determine whether survival of allogeneic hematopoietic cell transplantation (allo-HSCT) recipients, that develop GvHD, has improved over time.[2]

After an evaluation of 2,905 patients who had received a transplant between 1999 and 2012 and developed grade II-IV acute GvHD (aGvHD) within 100 days after allo-HSCT, they found a decrease in the proportion of grade III-IV disease from 56% between 1999-2001 to 37% between 2006-2012. A significant improvement in overall survival (OS) and a reduction in treatment-related mortality (TRM) were only noted among patients treated with tacrolimus-based GvHD prophylaxis.[2]

2. Khoury H.J. et al., Improved survival after acute graft-versus-host disease diagnosis in the modern era. Haematologica. 2017 May; 102(5): 958–966. DOI: 10.3324/haematol.2016.156356 *(free download)*

Pathogenesis of acute graft-versus-host disease: from intestinal microbiota alterations to donor T cell activation *(free download)*

In this review Zeiser R et al., Department of Hematology, Oncology and Stem Cell Transplantation, Freiburg University Medical Centre, Freiburg, DE, discuss recent insights into the pathogenesis of aGvHD.

Early research focused on the inhibition of T-cell receptor (TCR) activation (e.g. calcineurin inhibitors, cyclophosphamide); T-cell co-stimulation (e.g. abatacept to block CD28-mediated co-stimulation); and proinflammatory cytokines (e.g. inhibition of JAK1/2 by ruxolitinib).[3]

More recently, research has analyzed the influence of microbiome on GvHD initiation. The authors highlighted results from translational studies in mice which has allowed to identify potential targets to treat GvHD. Among those targets are intestinal stem cells (ISCs) and Paneth cells or strategies to protect the gut and promote intestinal integrity. Also, some microbiota-derived metabolites, like butyrate, seem to mitigate GvHD. Other promising targets are represented by microRNAs (miRs). MiRs relevant for GvHD which can be inhibited to decreased GvHD severity.[3]

3. Zeiser R. et al., Pathogenesis of acute graft-versus-host disease: from intestinal microbiota alterations to donor Tcell activation. Br J Haematol. 2016 Oct;175(2):191-207. DOI: 10.1111/bjh.14295 *(free download)*

Novel targets in the treatment of chronic graft-versus-host disease

In this review Im et al., Division of Hematology/Oncology, Department of Medicine, University of Pittsburgh Cancer Institute and UPMC Cancer Centers, Pittsburgh, US, summarize the novel therapeutic targets in chronic GvHD (cGvHD).

Many new agents target the T-cell signaling pathways. Examples are inhibitors of the JAK-STAT pathway (e.g. Ruxolitenib) and proteasome inhibitors such as Bortezomib. Targeting T-cell migration with sphingosine 1-phosphate (S1P) receptor modulators, as Fingolimod and Ponesimod, led to a reduction of circulating peripheral lymphocytes. Other new agents, such as abatacept and belatacept, are CTLA4-Ig fusion proteins that block T-cell co-stimulatory pathways by binding to CD80 and CD86 with a higher affinity than CD28.[4]

Also, inhibition of B-cell signaling pathways are currently investigated by anti-CD20 monoclonal antibodies such as rituximab, and BTK/ITK inhibitors such as ibrutinib. Similarly, Syk inhibitors fostamatinib and entospletinib are being evaluated in patients with cGVHD bothas monotherapy and in combination with steroids as first-line therapy for cGVHD.[4]

Furthermore, non-lymphocyte targets such as neutrophil elastase inhibitor (AZD9668), hedgehog inhibitors (vismodegib and sonidegib) are being studied in clinical trials as prophylaxis or treatment for steroid-refractory cGVHD with fibrotic or sclerodermatous manifestations.[4]

4. Im A. et al., Novel targets in the treatment of chronic graft-versus-host disease. Leukemia. 2017 Mar;31(3):543-554. DOI: 10.1038/leu.2016.367