Concomitant Ruxolitinib and Ibrutinib for Graft-Versus-Host Disease (GVHD): The First Reported Use in Pediatric Patients

Thomas A. Gagliardi 1, Jordan Milner 1, Mitchell S. Cairo 2, Amir Steinberg 1

1. Hematology and Oncology, Westchester Medical Center, New York Medical College, Valhalla, USA
2. Hematology and Oncology, Maria Fareri Children’s Hospital, New York Medical College, Valhalla, USA

Corresponding author: Thomas A. Gagliardi, ttagliardi@student.nymc.edu

Abstract

Allogeneic hematopoietic stem cell transplant (alloH SCT) can be a life-saving treatment option for patients with hematological disorders. Unfortunately, 50%-70% of patients who undergo alloH SCT develop a complication known as graft-versus-host disease (GVHD) [1]. During GVHD, donor T and B lymphocytes become activated by antigens-presenting cells due to human leukocyte antigen (HLA) differences in recipient tissue. Subsequently, cellular and inflammatory factors damage target organs, especially the skin, gastrointestinal tract, lungs, and liver. In the past, tissue damage that occurred within 100 days of transplant had been deemed acute GVHD (aGVHD), while fibrosis affecting any organ after 100 days post-alloH SCT was called chronic GVHD (cGVHD) [2]. Today, it is the acuity of GVHD that determines whether it is deemed acute or chronic GVHD. The first-line treatment of both aGVHD and GVHD is typically corticosteroids, which suppress the hyperactive immunological response. However, steroid-refractory GVHD has provided a challenge for patients and providers and led to the Food and Drug Administration (FDA) approval of ruxolitinib (Jakafi), ibrutinib (Imbruvica), and subsequently belumosudil (Rezurock).

Introduction

Allogeneic hematopoietic stem cell transplant (alloH SCT) can be a life-saving treatment option for patients with hematological disorders. Unfortunately, 50%-70% of patients who undergo alloH SCT develop a complication known as graft-versus-host disease (GVHD) [1]. During GVHD, donor T and B lymphocytes become activated by antigens-presenting cells due to human leukocyte antigen (HLA) differences in recipient tissue. Subsequently, cellular and inflammatory factors damage target organs, especially the skin, gastrointestinal tract, lungs, and liver. In the past, tissue damage that occurred within 100 days of transplant had been deemed acute GVHD (aGVHD), while fibrosis affecting any organ after 100 days post-alloH SCT was called chronic GVHD (cGVHD) [2]. Today, it is the acuity of GVHD that determines whether it is deemed acute or chronic GVHD. The first-line treatment of both aGVHD and GVHD is typically corticosteroids, which suppress the hyperactive immunological response. However, steroid-refractory GVHD has provided a challenge for patients and providers and led to the Food and Drug Administration (FDA) approval of ruxolitinib (Jakafi), ibrutinib (Imbruvica), and subsequently belumosudil (Rezurock).

Case Presentation

Case 1

Patient 1 was a four-year-old female diagnosed with natural killer (NK) cell dysfunction who underwent alloH SCT with cells from a 9/10 National Marrow Donor Program (NMDP) donor and subsequently developed chronic GVHD (cGVHD) of the skin and gut. This cGVHD was refractory to steroids and ibrutinib but improved with the administration of concomitant ruxolitinib and ruxolitinib. Patient 2 was a one-year-old male with sickle cell anemia. The patient was transplanted under a haploidentical protocol from the mother but developed bronchiolitis obliterans organizing pneumonia (BOOP) and pathology-confirmed GVHD. This BOOP was steroid-refractory and resolved with the administration of concomitant ruxolitinib and ruxolitinib. To our knowledge, this is the first reported use of concomitant ruxolitinib and ibrutinib in pediatric patients. The combination was well tolerated with no significant adverse events. Neither patient had to discontinue these drugs. We propose a further investigation into this dual therapy in cGVHD either compared to steroids or as a second-line option.

Concomitant Ruxolitinib and Ibrutinib for Graft-Versus-Host Disease (GVHD): The First Reported Use in Pediatric Patients
**Case 2**

Patient 2 was a one-year-old male with sickle cell anemia who underwent alloHSCT utilizing a haploidentical protocol from the mother (source: bone marrow). The relevant treatment modalities and diagnoses in a timeline in relation to alloHSCT during this patient’s care are depicted in Table 2 and are described in this paragraph. A conditioning regimen was implemented and is depicted in Table 2. Fludarabine was given intravenously at a dose of 50 mg/m² on days -15 through -11. Busulfan was given at a dose of 2 mg/kg intravenously on days -5 through -2. Thiotepa was given on day -2 at a dose of 10 mg/kg IV. Cyclophosphamide was given at a dose of 50 mg/kg IV with mesna on days -5 and -4. Thymoglobulin was given at a dose of 2 mg/kg on days -5 through -2 (4). The patient received a CD34+ enrichment with T cell addback of 2 × 10^6 CD3/kg. The patient began to exhibit constitutional symptoms including fever and diarrhea, and a computed tomography (CT) scan of the chest was performed that raised concern for an infiltrative process. These symptoms did not improve with the addition of broad-spectrum antibiotics. The patient was diagnosed with bronchiolitis obliterans organizing pneumonia (BOOP) on day +21 following a lung biopsy that was sent to pathology. After a review of the pathology report by an outside institution, the possibility of thrombotic microangiopathy (TMA) was raised in the context of high lactate dehydrogenase (LDH) and low platelets in the blood. To treat the BOOP, a regimen of fluticasone, azithromycin, and montelukast (FAM) was initiated (7). Systemic steroids were not initiated at this time. Despite FAM, the BOOP persisted as confirmed by a lung biopsy on day +87 and was considered as GVHD at this point. On day +41, the patient was placed on ibrutinib 140 mg daily and ruxolitinib 2.5 mg BID. On day +44, the patient was initiated on ECP twice per week. Symptoms began to improve after one month of this therapy. The duration of the lungs appeared stable on computed tomography (CT) imaging following the initiation of ibrutinib, ruxolitinib, and ECP. Beginning on day +477, the dose of ruxolitinib was tapered in half of the patient. On day +534, the patient was tapered off ruxolitinib by day +534, ibrutinib by day +618, and ECP by day +628 (Table 2). No adverse events were reported for the combination of ruxolitinib and ibrutinib in this patient.

**Table 2:** Timeline of treatment modalities and diagnoses in relation to alloHSCT in patient 2.

| Day | -15 | -11 | -9 | -7 | -5 | -3 | -2 | 0 | 217 | 407 | 411 | 414 | 477 | 534 |
|-----|-----|-----|----|----|----|----|----|---|-----|-----|-----|----|----|-----|
| Treatment modality or diagnosis | Fludarabine | 30 mg/m² | | | | | | | | | | | | |
| | Busulfan | 2 mg/kg | | | | | | | | | | | | |
| | Thiotepa | 10 mg/kg | | | | | | | | | | | | |
| | Cyclophosphamide | 50 mg/kg, with mesna; Thymoglobulin 2 mg/kg | | | | | | | | | | | | |
| | Cyclophosphamide | 50 mg/kg, with mesna; Thymoglobulin 2 mg/kg | | | | | | | | | | | | |
| | Thymoglobulin | 2 mg/kg | | | | | | | | | | | | |
| Diagnosis of GVHD | | | | | | | | | | | | | | |
| | BOOP | | | | | | | | | | | | | |
| | BOOP persistence confirmed by pathology - considered cGVHD | | | | | | | | | | | | | |
| Ibrutinib | 140 mg daily initiated; ruxolitinib 2.5 mg BID initiated | | | | | | | | | | | | | |
| ECP | Twice per week initiated | | | | | | | | | | | | | |
| Ruxolitinib | Tapered to 0 mg BID completed; ruxolitinib discontinued | | | | | | | | | | | | | |

**Discussion**

We believe this to be the first reported use of concomitant therapy of ruxolitinib and ibrutinib to treat cGVHD in the pediatric population. We identified one paper reporting on ruxolitinib for cGVHD that briefly described in this paragraph. A conditioning regimen was implemented and is depicted in Table 2. Fludarabine was given intravenously at a dose of 50 mg/m² on days -15 through -11. Busulfan was given at a dose of 2 mg/kg intravenously on days -5 through -2. Thiotepa was given on day -2 at a dose of 10 mg/kg IV. Cyclophosphamide was given at a dose of 50 mg/kg IV with mesna on days -5 and -4. Thymoglobulin was given at a dose of 2 mg/kg on days -5 through -2 (4). The patient received a CD34+ enrichment with T cell addback of 2 × 10^6 CD3/kg. The patient began to exhibit constitutional symptoms including fever and diarrhea, and a computed tomography (CT) scan of the chest was performed that raised concern for an infiltrative process. These symptoms did not improve with the addition of broad-spectrum antibiotics. The patient was diagnosed with bronchiolitis obliterans organizing pneumonia (BOOP) on day +21 following a lung biopsy that was sent to pathology. After a review of the pathology report by an outside institution, the possibility of thrombotic microangiopathy (TMA) was raised in the context of high lactate dehydrogenase (LDH) and low platelets in the blood. To treat the BOOP, a regimen of fluticasone, azithromycin, and montelukast (FAM) was initiated (7). Systemic steroids were not initiated at this time. Despite FAM, the BOOP persisted as confirmed by a lung biopsy on day +87 and was considered as GVHD at this point. On day +41, the patient was placed on ibrutinib 140 mg daily and ruxolitinib 2.5 mg BID. On day +44, the patient was initiated on ECP twice per week. Symptoms began to improve after one month of this therapy. The state of the lungs appeared stable on computed tomography (CT) imaging following the initiation of ibrutinib, ruxolitinib, and ECP. Beginning on day +477, the dose of ruxolitinib was tapered in half of the patient. On day +534, the patient was tapered off ruxolitinib by day +534, ibrutinib by day +618, and ECP by day +628 (Table 2). No adverse events were reported for the combination of ruxolitinib and ibrutinib in this patient.

| Day | -15 | -11 | -9 | -7 | -5 | -3 | -2 | 0 | 217 | 407 | 411 | 414 | 477 | 534 |
|-----|-----|-----|----|----|----|----|----|---|-----|-----|-----|----|----|-----|
| Treatment modality or diagnosis | Fludarabine | 30 mg/m² | | | | | | | | | | | | |
| | Busulfan | 2 mg/kg | | | | | | | | | | | | |
| | Thiotepa | 10 mg/kg | | | | | | | | | | | | |
| | Cyclophosphamide | 50 mg/kg, with mesna; Thymoglobulin 2 mg/kg | | | | | | | | | | | | |
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| Ibrutinib | 140 mg daily initiated; ruxolitinib 2.5 mg BID initiated | | | | | | | | | | | | | |
| ECP | Twice per week initiated | | | | | | | | | | | | | |
| Ruxolitinib | Tapered to 0 mg BID completed; ruxolitinib discontinued | | | | | | | | | | | | | |

**Table 1:** Timeline of treatment modalities and diagnoses in relation to alloHSCT in patient 1.

| Day | -15 | -11 | -9 | -7 | -5 | -3 | -2 | 0 | 148 | 189 | 490 | 883 | 951 | 980 | 1,172 |
|-----|-----|-----|----|----|----|----|----|---|-----|-----|-----|----|----|-----|------|
| Treatment modality or diagnosis | Alemtuzumab | 2 mg/m² | | | | | | | | | | | | | |
| | Alemtuzumab | 6 mg/m² | | | | | | | | | | | | | |
| | Alemtuzumab | 20 mg/m² | | | | | | | | | | | | | |
| | Fludarabine | 30 mg/m² | | | | | | | | | | | | | |
| | Melphalan | 140 mg² | | | | | | | | | | | | | |
| | CYC | | | | | | | | | | | | | |
| | ECP | | | | | | | | | | | | | |
| | Cyclophosphamide | 50 mg/kg, with mesna; Thymoglobulin 2 mg/kg | | | | | | | | | | | | | |
| | Cyclophosphamide | 50 mg/kg, with mesna; Thymoglobulin 2 mg/kg | | | | | | | | | | | | | |
| | Thymoglobulin | 2 mg/kg | | | | | | | | | | | | | |
| | CYC | | | | | | | | | | | | | |
| | ECP | | | | | | | | | | | | | |
| aGVHD of the skin | | | | | | | | | | | | | | |
| BOOP | | | | | | | | | | | | | | |
| GVHD of the skin | | | | | | | | | | | | | | |
| GVHD of the skin and gut | | | | | | | | | | | | | | |
| GVHD of the skin, gut, and TMA | | | | | | | | | | | | | | |
| GVHD of the skin, gut, and TMA - began | | | | | | | | | | | | | | |
| GVHD persistence - began | | | | | | | | | | | | | | |
| GVHD persistence - began | | | | | | | | | | | | | | |
| GVHD persistence - began | | | | | | | | | | | | | | |

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totoxicity, especially diarrhea, bleeding issues, high blood pressure, atrial fibrillation, and cytopenias for ibrutinib [9]. As one can see, these agents may share similar toxicities. By carefully monitoring symptoms and dose-adjusting, if needed, these side effects may be manageable. Additionally, our pediatric population may be better able to tolerate the adverse effects of combining both medications. We understand that only a randomized trial will truly be able to answer this important question of efficacy as well as safety. It would be meaningful to see data comparing these agents to steroids as front-line therapy for new chronic GVHD.

Our team was concerned with the toxicity of steroids and the concern for dependency on steroids in the pediatric population. Long-term steroid use can have debilitating effects on children, such as stunted growth, and effects on natural development. These issues are not relevant to the adult population. Children may also experience the same toxicities that adults can suffer with steroids, such as high blood pressure, bone strength and growth, hyperglycemia, and heart and liver toxicity, threatening long-term health. Although the novel immunosuppressive therapies ruxolitinib and ibrutinib are more expensive than steroids, one must keep in mind the financial costs of long-term steroid exposure, with long-term progression over the course of one’s lifetime, especially in the pediatric population [10]. Thus, ruxolitinib or ibrutinib alone, or in combination as our group demonstrated, could be a potential treatment approach for newly diagnosed chronic GVHD in the pediatric population.

Further research should be done to better understand how the combined therapy of ruxolitinib and ibrutinib compares in the treatment of GVHD to steroids. It is noteworthy that the FDA recently approved belumosudil (Rezurock) for GVHD (July 2021). Belumosudil is a selective Rho-associated coiled-coil containing protein kinase 2 (ROCK2) inhibitor [11]. This decreases inflammation by decreasing the activation of signal transducer and activator of transcription 3 (STAT3), preventing the IL-6/STAT3 complex and thus downregulating Th17 and Thb cells. The inhibition of ROCK2 also increases the phosphorylation of signal transducer and activator of transcription 5 (STAT5), upregulating Treg cells to decrease inflammation. Belumosudil also decreases fibrosis, which has been seen in animal models as decreased collagen deposition around the bronchioles and delayed progression of scleroderma [11]. This illustrates yet another pathway of inflammation and fibrosis that physicians can target in the therapy of GVHD.

The future of GVHD management may benefit from “cocktails” of two, three, or even more drugs targeting distinct pathways to elicit a synergistic response against this common complication of bone marrow transplants. Since both the JAK and BTK signaling pathways appear requisite for the development of GVHD, it makes sense that targeting both at the same time could elicit a stronger response than selecting either at a time, hence our use of concomitant ruxolitinib and ibrutinib. However, the financial toxicity of these drugs is to be considered. These immunosuppressive medications can cause a substantial financial burden on patients and society, so the judicious use of such medication cocktails is recommended. On the horizon are additional therapies designed for GVHD. Azacitidine, a humanized antibody against macrophage colony-stimulating factor receptor (CSF-R), is in an active phase II clinical trial to dampen pulmonary fibrosis in cGVHD [12]. Abatacept (Orencia) is an immunosupulatory fusion protein currently being investigated for its efficacy in treating steroid refractory GVHD [13]. Abatacept recently became the first drug FDA approved specifically for aGVHD prophylaxis in December 2021 but is contraindicated in the presence of a JAK inhibitor, such as ruxolitinib. With the rapid development of these new therapies and the strategic combination of existing ones, the future of patients with cGVHD has solid grounds for hope.

Conclusions
Pediatric patients suffering from steroid refractory chronic graft versus-host disease (cGVHD) may be effectively treated with concomitant ruxolitinib and ibrutinib without serious adverse effects related to the dual administration of these drugs. The suppression of both the JAK and BTK pathways simultaneously appears to reduce GVHD progression. Multidrug therapy can be considered to manage remaining cases of cGVHD while considering the financial burden that these drugs may have on patients and their families. Large-scale studies should be conducted to further evaluate the safety and efficacy of our proposed combination therapy. More therapies are likely to be approved for GVHD management, making it important for physicians to stay well-read on the changing landscape of GVHD treatment.

Additional Information
Disclosures
Human subjects: Consent was obtained or waived by all participants in this study. New York Medical College Oncology Institutional Review Board (IRB) issued approval protocol #14622. A retrospective case review of Chronic Graft vs Host Disease (cGVHD) treated with novel immunotherapy agents Brutinidil and Ruxolitinib,* New York Medical College, Westchester Medical Center, 14622, has been verified by the New York Medical College Medical Oncology IRB as exempt according to 45CFR46.101(b) (4). (4) Secondary Research Uses of Data or Specimens on 10/20/2021. The following items associated with this protocol have been approved: protocol: 09/15/2021 retrospective cGVHD protocol_clean_09.10.21.docx; data collection tool: 09/15/2021. Case Report cGVHD Data_09.15.21.xlsx; and memos: 07/26/2021 IRB Memo_14622_Response 07.19.21.pdf and 09/13/2021 IRB Memo_14622_Response 09.10.21_signed.pdf. This constitutes New York Medical College’s permission to initiate the referenced study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: Mitchell S. Cairo declare(s) personal fees from Novartis. Mitchell S. Cairo has received consultant fees from Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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