A Single Institution Experience of Bortezomib for GVHD in a Pediatric HSCT Population

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Abstract

Acute graft versus host disease (aGvHD) remains one of the most serious complications, occurring in about 30-70%, of allogeneic hematopoietic stem cell transplantation (HSCT) recipients. While about 40-60% of these recipients will respond to steroids as first line, there is no consensus on second line agents. The management of steroid-refractory (SR) and steroid dependent (SD) GVHD after HSCT continues to be challenging. In the absence of clinical trials, treatment in most cases is based on individual physician or center experience. Herein, we present our institutional experience with the use of bortezomib, a first-generation reversible proteasome inhibitor, in SD aGvHD.

Introduction

Corticosteroids remain first-line therapy for GVHD[1]. Although several salvage therapeutic options for SR and SD GVHD exist, there is no consensus[6]. Consequences of prolonged steroid use is severe non-specific immunosuppression, potential loss of graft-versus-tumor (GVT) effect in patients with malignancy, and increased infection risk[1]. Salvage therapy is often selected based on adverse effect profile, patient's unique characteristics, drug availability, or institutional experience[1].

Bortezomib is a first-generation reversible proteasome inhibitor that has shown efficacy in murine aGVHD models leading to clinical trials and use in adult HSCT. Bortezomib inhibits nuclear factor-kappa B (NF-$\varkappa$B) [1], resulting in inhibition of T- and B-cell activation and pro-inflammatory cytokine transcription[1,2]. It increases T-cell apoptosis, decreases expression of activation markers and receptors on T-cells, and decreases T-cell proliferation. Additionally, bortezomib aids in treating GVHD by preventing activation of DCs which mediate antigen presentation and cytokine transcription that ultimately causes organ damage in GVHD[1,2].

Basic science studies demonstrated that bortezomib has the effect of preserving GVT effect by allowing for persistence of T-regulatory cells thus promoting recipient T-cell reconstitution.[2]

Continuous administration of bortezomib after HSCT in pre-clinical studies resulted in cutaneous aGVHD reduction, associated with decreased IL-6 level[14]. Bortezomib administration resulted in the specific down-regulation of CXCR3, a skin-homing chemokine receptor, on donor $CD8^+$ T cells in a murine aGVHD model.[14]

Koreth *et al* reported on 45 adult patients with mMUD donors who received GVHD prophylaxis with bortezomib in addition to methotrexate and tacrolimus[2]. Grade 2-4 aGVHD was present in 22% and 29% developed cGVHD, with a 2-year OS of 64%[2]. Additionally, T-cell reconstitution was deemed favorable when compared with matched patients who received standard GVHD prophylaxis without bortezomib[2].

Miller *et al* demonstrated patients with SD and SR cGVHD while on bortezomib was able to wean from prednisone[2]. Pai*et al* evaluated SR cGVHD patients treated with bortezomib, documenting favorable responses including decreased sclerotic non-healing skin lesions and reduced diarrhea[2].

Herrera *et al* evaluated a combination of bortezomib and prednisone treatment of cGVHD [2]. A positive response reported in 80%, with 10% a complete response (CR) and the remainder had a partial response (PR). Best results were seen in the skin and gastrointestinal tract[2].

Further studies of bortezomib are needed in children and young adults to delineate its potential benefits and toxicities in this age group in terms of GVHD prophylaxis and treatment. Over a period of five years, five pediatric BMT patients at Sylvester Comprehensive Cancer Center at the University of Miami and Holtz Children's Hospital were treated with bortezomib as part of their treatment for SR and SD GVHD post-HSCT. We review these to provide proof of principle for potential future trials of this agent for SR and SD GVHD in pediatric HSCT.

CASE EXAMPLES

Case 1:

A 7-year-old male patient with high-risk AML developed initial gastrointestinal and ocular GVHD 23 days post-allogenic HSCT. He was initially on prednisone and sirolimus; first attempts included weaning him from prednisone with extracorporeal photopheresis (ECP), but he continued to have multiple skin GVHD flares with worsening manifestations to grade 4 aGVHD. Bortezomib was initiated due to continued steroid dependence (Table 1). Due to development of pancytopenia, dose reduction was required temporally, before increasing again. His skin lesions steadily improved, permitting bortezomib dose taper to discontinuation and discontinuation of prednisone with subsequently stopped all immune suppression.

Case 2:

A 4-year-old male patient with X-linked lymphoproliferative disorder and associated EBV-positive DLBCL presented with aGVHD of the skin on day +78 after haploidentical maternal HSCT. GVHD prophylaxis was with sirolimus. Steroids were initiated once GVHD developed. Unable to wean off steroids, bortezomib was initiated (Table 1), during which prednisone was weaned and eventually discontinued. Subsequently, all other immune suppression was discontinued. Later, he subsequently developed intervening liver GVHD at day +341 and restarted bortezomib, requiring a 50% dose reduction due to neutropenia. Upon neutrophil count recovery, the bortezomib dose was increased but, liver function did not improve. After five doses bortezomib was discontinued and pentostatin initiated. The patient was then successfully weaned from prednisone. Bortezomib showed promise in treatment of skin GVHD but had no effect on his liver GVHD.

Case 3:

A 1-year-old female with Radioulnar Synostosis and Amegakaryocytic Thrombocytopenia presented with SD aGVHD of the skin around day +177. The patient was started on prednisone and sirolimus. Attempts to wean from prednisone led to multiple skin GVHD flares. Rituximab was given without success. She was deemed underweight for ECP catheter placement, so bortezomib was initiated and increased as tolerated for total of 24 weekly doses (Table 1). There was initial PR to bortezomib, allowing wean of steroids; however, she was unable to completely discontinue prednisone. All bortezomib doses were well tolerated, with the only complications including delayed dose due to rhinovirus infection, and a temporary dose reduction due to pancytopenia. The patient ultimately continued to have skin flare-ups after the initial response, and bortezomib was discontinued.

Case 4:

A 19-year-old male with Ewing Sarcoma followed by treatment related MDS developed lung GVHD on day +451 after a MUD HSCT. GVHD therapy included sirolimus, prednisone, bortezomib, solumedrol, rituximab, and ECP. He responded well to bortezomib, allowing wean from prednisone (Table 1). He subsequently

developed pancytopenia requiring bortezomib dose reduction and eventual discontinuation. The pancytopenia improved after discontinuation of bortezomib and he was able to remain steroid-free. He later developed a GVHD flare and was restarted on bortezomib along with prednisone, while remaining on sirolimus. Bortezomib was again discontinued due to pancytopenia and development of peripheral neuropathy. ECP was initiated with demonstrable initial respiratory response, but he subsequently experienced acute respiratory failure and succumbed to multi-organ failure.

Case 5:

A 14-year-old female with MDS underwent a haploidentical HSCT complicated by SD aGVHD of the liver. This was preceded by grade 1 steroid-responsive aGVHD of the gut, B-K viremia and viruria, HHV-6 viremia, CMV viremia and hypertension. Throughout her HSCT course, she had aGVHD flares of skin and gut due to non-compliance with her immunosuppression. Each flare was steroid responsive. Shortly after day +300, she developed worsening transaminitis and skin GVHD that was SD. Bortezomib was started with successful steroid wean initiated within one week of her initial bortezomib dose (Table 1). Over the subsequent three months, while receiving weekly bortezomib, she was successfully weaned from steroids.

Conclusion

Our single institutional case series experience with bortezomib for SR and SD GVHD after pediatric HSCT, serves as proof of principle for tolerability, potential efficacy and development of future clinical trials. Among dose-limiting toxicities, pancytopenia was observed in almost all patients to varying degrees. No patients experienced infections or prolonged complications, and all had resolution of pancytopenia following dose reduction of bortezomib. Most patients tolerated bortezomib well, without serious adverse events. One patient experience peripheral neuropathy.

Though limited by sample size and single-center non-controlled anecdotal experience, we believe that this series is supportive of the possibility that bortezomib's use in pediatric patients could be effective as second-line, steroid-weaning therapy in SD or SR GVHD. Bortezomib appears to be more effective in skin GVHD, and some response with liver GVHD. Our goal in the future is to create a clinical trial to evaluate the tolerability and efficacy of bortezomib in SR and SD GVHD and to standardize a dosing regimen for pediatric patients.

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