

The Impact of Bortezomib in Renal Transplantation

Abstract

Kidney transplantation is one of the most common solid organ transplants that improves quality of life and promotes longevity of the patients. However, the access to transplantation is limited by the shortage of deceased donor organs and the presence of HLA antibodies prior transplantation. Many efforts have been made to promote living kidney donation due to the better survival rates, and desensitization protocols have been developed in order to abrogate or reduce the titers of anti-HLA antibodies. Several regimens can be used, including pre-transplantation induction therapy and post-operative immunosuppression to prevent graft rejection, reduce morbidity and complications.

Immunosuppressant drugs currently used against allojection are calcineurin inhibitors, corticosteroids, antimetabolites, and mTOR inhibitors. Unmet treatment needs have recently hastened investments in alternative approaches. Along this line, bortezomib, which is a proteasome inhibitor and is already approved by FDA for the treatment of multiple myeloma, has been proposed for conversion of the sensitized status of the patients. This agent is now also used as a rescue treatment for antibody-mediated rejection (AMR). In this mini-review, I aim to discuss recent studies on bortezomib in renal transplant recipients with donor-specific antibodies (DSA) and increased risk for AMR. The role of the drug is not clearly defined on the course of late AMR, awaiting final results from the BORTEJECT trial, and large multicenter dose-response studies are required.

Keywords: Bortezomib; Proteasome; Immunosuppression; Sensitization; Kidney transplant

Mini Review

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Abbreviations: AMR: Antibody-Mediated Rejection; cPRA: Calculated Panel Reactive Antibody; SAB: Single Antigen Beads; DSA: Donor Specific Antibodies; IVIG: Intravenous Immunoglobulin; ATG: Anti-Thymocyte Globulin; PLEX: Plasma Exchange; GFR: Glomerular Filtration Rate

Introduction

Kidney transplantation increases life expectancy and quality, and is overall less cost effective compared to dialysis [1,2]. Critical points in transplantation process are the limited deceased donor organs and the high sensitization of the patients to a previous exposure to "non-self" proteins, such as multiple blood transfusions, previous transplants, and number of pregnancies. Many attempts have been made to encourage living kidney donation because of the improved survival rates but there is still much that can be done to optimize education, access and care. Paired kidney exchange programs are activated to find suitable living donors [3,4].

The Luminex-based screening and the sensitive Single Antigen Beads (SAB) are tests to detect HLA antibodies and sensitized subjects result with a high calculated Panel Reactive Antibody (cPRA). In addition, the C1q test assesses donor-specific anti-HLA antibodies (DSA) with complement-binding capacity [5]. The antibodies that fix complement play a role in the acute presentation of c4d positive antibody-mediated rejection (AMR)

and are difficult to eliminate or prevent their activity. Nevertheless, non-complement binding antibodies can be equally deleterious leading to chronic AMR and transplant glomerulopathy [6].

Several desensitization protocols have been empirically developed in order to remove anti-HLA antibodies. Satisfactory outcomes in many cases have been achieved with plasmapheresis, rituximab (anti-CD20) and intravenous immunoglobulin (IVIG) desensitization procedures. Determining initial titer and DSA specificity are essential for successful desensitization [7]. Before surgery induction therapy (anti-thymocyte globulin (ATG) or alemtuzumab) and post-transplant life-long immunosuppression are given to prevent allograft rejection. The most common types of maintenance immunosuppressive drugs prescribed to kidney recipients are calcineurin inhibitors (cyclosporine, tacrolimus), corticosteroids (methylprednisolone, prednisone), antimetabolites (mycophenolate mofetil, azathioprine), and mTOR inhibitors (sirolimus, everolimus). The choice of the treatment depends on the status of the patient as well as on the training and experience of the transplantation center.

Bortezomib is now being investigated as a therapeutic agent to get rid of anti-HLA antibodies. Here, I briefly present this molecule and critically discuss advantages and disadvantages of using this compound in the treatment of kidney transplant recipients as from recent clinical studies.

Bortezomib: a key player in cancer and desensitization therapy

Bortezomib (Velcade, Millennium Pharmaceuticals Inc.) is a proteasome inhibitor drug approved by FDA in 2008 for initial treatment of patients with multiple myeloma, a clonal B-cell malignancy, based on the results obtained from the SUMMIT trial [8]. Later in 2014 it has also been approved for the treatment of patients with relapsed multiple myeloma and mantle cell lymphoma.

Structural characteristic of bortezomib is the boron atom that binds the catalytic site of the 26S proteasome with high affinity and specificity. The role of proteasome in the cell consists in the regulation of protein expression, degradation of ubiquitinated proteins and removal of abnormal or misfolded proteins. The proteasome inhibition may prevent degradation of pro-apoptotic factors, allowing activation of programmed cell death in cancer cells dependent upon inhibition of pro-apoptotic pathways. It has been seen that bortezomib up-regulates NOXA, a pro-apoptotic member of the Bcl-2 protein family, and causes apoptotic cell death. Bortezomib also suppresses the NF- κ B signaling pathway and consequently causes down-regulation of anti-apoptotic target genes [9].

Data support that bortezomib causes a dramatic change in the levels of the mitochondrial-based apoptotic pathway and the consequent mitochondrial and endoplasmic reticulum damage may contribute to the side effects of the drug [10]. The most common adverse effects associated with bortezomib are gastrointestinal events, asthenia, hematological toxicity, and peripheral neuropathy [11]. The information related to the bortezomib tolerance mainly comes from the APEX Phase III trial, which compared the efficacy of bortezomib versus dexamethasone in refractory or relapsed multiple myeloma, and from the VISTA trial which compared melphalan and prednisone with or without bortezomib in previously untreated patients with multiple myeloma [12,13].

Bortezomib has strong suppressive effects on humoral immunity since it triggers apoptosis of CD138+CD20-bone marrow-derived plasma cells and it inhibits antibody production from mature plasma cells [14]. Furthermore, the combined administration of rapamycin and bortezomib abrogates the proliferation of memory B cells preserving the survival of CD4+FoxP3+ regulatory T cells and limits the production of IL-4, IL-6, IL-10, and IFN- γ [15].

Several studies have questioned the effectiveness of a bortezomib-based treatment in patients experiencing severe AMR [16-22]. In a study including four kidney transplant recipients with subacute AMR and persistent DSA, only one dose of intravenous bortezomib (1.3 mg/m²) used as a sole drug did not significantly decrease DSA in a 5 months follow-up [18]. On the other hand, a more recent report supports the beneficial effects of bortezomib use (1.3 mg/m²) on 4 out of 6 patients that achieved reduction of DSA, biopsy proven resolution of AMR and stable renal function [20]. Bortezomib has proved as an effective desensitizing agent in 9 over 11 patients treated with a combination of bortezomib and plasma exchange (PLEX). It decreased both DSA and non-DSA anti-HLA antibodies with stable graft function whereas 2 patients maintained strong HLA antibodies. Four patients had

reoccurrence of anti-HLA antibodies after the initial reduction [17].

Bortezomib administered in two highly sensitized kidney recipients caused more than 50% decrease of complement fixing anti-HLA antibodies. Dexamethasone was added to bortezomib to the second cycle of treatment to enhance efficacy [22]. In pre-transplant setting, bortezomib in combination with rituximab desensitized a kidney transplant candidate decreasing the cPRA from 57% to 31%. The patient received a cadaveric donor kidney with a single weak DSA that became undetectable post-transplant [23].

The BORTEJECT study aims to refine the role of bortezomib in late AMR. The study is performed in Vienna, Austria, sponsored by the Medical Universities of Vienna and Innsbruck and started in December 2013 with estimated completion in February 2017. In this single-center phase II trial, 1,000 kidney transplant recipients are enrolled. DSA-positive patients will undergo kidney allograft biopsy to detect morphological features consistent with AMR. Forty-four patients with late AMR are eligible to be included in a randomized double-blind placebo-controlled parallel-group intervention trial. Patients in the active group receive two cycles of bortezomib.

The primary end point is the estimated glomerular filtration rate (GFR) in 24 months. Secondary endpoints are designed to answer specific questions, such as the levels of DSA, protein excretion, GFR, graft and patient survival, and the development of acute and chronic morphological lesions in 24-month protocol biopsies [24]. Preliminary results of the BORTEJECT study after AMR screening on 714 recipients showed that circulating DSA may not always associate with AMR diagnosis, especially in recipients with weak antibodies [25]. Of note, carfilzomib (Kymriah, Onyx Pharmaceuticals, Inc.) is another selective proteasome inhibitor, which is FDA drug approved in 2012 and it could be used for selected patients with relapsed multiple myeloma and renal impairment [9,26].

Final remarks

Comparing new treatment modalities for kidney transplant patients against old ones, reveals bortezomib a potential desensitization therapeutic strategy. Bortezomib is the first approved proteasome inhibitor used as antineoplastic drug but also seen to reverse early and late antibody-mediated rejection. There are issues still unsolved, such as the interpretation of low titers of DSA, the subclinical AMR and its transition to chronic allograft injury. Most clinical trials are single-center, with low number of subjects, with different trial plans, hence their results are discordant and do not allow to clarify the hierarchical importance and biological function of plasmapheresis, IVIG, rituximab and/or bortezomib. Since bortezomib was used in combination with other drugs, its specific therapeutic role could not be firmly established. Is the DSA lowering due to clinical use of bortezomib or is just part of the natural clinical course of the patient? Bortezomib may be successful for altering complement fixing HLA-antibodies [22,27].

We need more clinical data to clarify the pathological significance of the presence DSA in AMR [28], the modulation of HLA antibodies due to bortezomib is durable and classify better

the patients that can have optimal response to the drug [29-31]. Given the limited experience and lack of long-term follow-up, bortezomib may be best utilized at the moment as an adjunct to other established therapies. Well-designed, prospective, randomized and controlled studies should evaluate the safety and the efficacy profile, including dosage, of bortezomib, in the treatment of kidney transplant patients with concurrent better graft outcome.

Conflict of interest

The author has no conflict of interest to report.

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