Ann Hematol (2016) 95:1751–1756
DOI 10.1007/s00277-016-2804-x

REVIEW ARTICLE

Bortezomib therapy in patients with relapsed/refractory acquired thrombotic thrombocytopenic purpura

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Received: 3 June 2016 / Accepted: 28 August 2016 / Published online: 3 September 2016

Abstract Therapeutic plasma exchange (TPE) has dramatically improved the prognosis of acquired thrombotic thrombocytopenic purpura (TTP), and TPE and corticosteroids are the mainstays of treatment of acquired TTP. However, a subset of patients may remain refractory to this treatment modality, or have an initial response but relapse after the discontinuation of TPE during the follow-up. While managing patients with relapsed/refractory acquired TTP, there are several therapeutic maneuvers, which can be considered. Recently, there came some papers regarding the use of bortezomib in relapsed or refractory acquired TTP, and in this review, this indication of bortezomib was evaluated along with the current data available. In seven published papers, 12 patients with relapsed/refractory acquired TTP received bortezomib, of which 11 survived the acute episodes and maintained remission. Bortezomib may serve as an adjunct treatment, but prospective trials are needed to determine the dosing, administration route, and the treatment schedule of this treatment option in patients with relapsed/refractory TTP.

Keywords Bortezomib · Refractory · Relapsed · Thrombotic microangiopathy · Thrombotic thrombocytopenic purpura

Introduction

Acquired thrombotic thrombocytopenic purpura (TTP) is characterized by microangiopathic hemolytic anemia (MAHA) and thrombocytopenia without an obvious cause. Although TTP was first characterized by the classical diagnostic pentad, it can present without renal failure, neurologic deficits, and fever [1]. If left untreated, it is a fatal disease, but therapeutic plasma exchange (TPE) has dramatically improved the prognosis of acquired TTP, decreasing the mortality rate from 90 % to less than 20 % [2]. TPE and corticosteroids are the mainstays of treatment of acquired TTP; however, a subset of patients may remain refractory to this treatment modality, or have an initial response but relapse after the discontinuation of TPE during the follow-up.

In patients with relapsed/refractory acquired TTP, there are some therapeutic maneuvers which can be considered [3]. Recently, there came some publications regarding the use of bortezomib in relapsed or refractory acquired TTP [4–10], and this review mainly focuses on the current data for bortezomib use in managing patients with relapsed/refractory acquired TTP.

The management of relapsed/refractory acquired TTP

There is limited information or consensus available on the management of relapsed/refractory acquired TTP. While managing TPE refractory patients, TPE may be intensified to 1.5 plasma volume, and even twice-daily TPE can be used [11]. In newly diagnosed patients, prednisone with a dose of 1 mg/kg per day is usually started upfront together with TPE [12], and in cases who are refractory to TPE plus corticosteroids, the administration of high-dose methylprednisolone 1 g per day for 3 days can be the choice of treatment [13]. Other treatment options in patients with relapsed/refractory TTP may include rituximab, vincristine, cyclophosphamide, cyclosporine A (CSA), and splenectomy [14–18].

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Bortezomib

Bortezomib a first-in-class proteasome inhibitor (PI) has been extensively studied either alone or in combination with other agents for the treatment of multiple myeloma (MM) both in the frontline and relapsed settings [19]. Bortezomib works in the ubiquitin-proteasome pathway of cellular protein homeostasis by blocking the action of the 26S proteasome, a multicatalytic enzyme that degrades abnormal or misfolded proteins targeted for destruction, particularly those involved in cell cycling and gene transcription. Because these proteins are more abundant during the processes of oncogenesis, they are key in cancer survival; proteasome inhibition in cancer cells leads to cell apoptosis and is a target for therapy [20].

Bortezomib in clinical practice

In the daily hematology practice, apart from its use in MM and other plasma cell disorders [21], bortezomib can be administered in patients with lymphoproliferative neoplasms including mantle cell lymphoma [22].

In addition to that, bortezomib also appears to be a promising early desensitizing agent in the setting of kidney transplantation with high short-term success rates [23]. Moreover, in patients with liver transplant, bortezomib has demonstrated an ability to significantly reduce pathologic antibody titers and promote long-term organ survival in those refractory to rituximab therapy [24]. However, randomized trials are still needed to more conclusively demonstrate its effectiveness and optimal administration time in relation to transplant surgery.

When treating patients with MM, the daily dose of bortezomib is 1.3 mg/m^2, and it can be used on days 1, 4, 8, 11, and repeated every 21 days, or the same dose can be administered on days 1, 8, 15, 22, and repeated every 4 weeks [21].

Bortezomib therapy is not without toxicities, and various adverse events (AEs) can be observed during this treatment, which may need some dosing modifications [25]. The initial administration route of bortezomib was intravenous, but recently, subcutaneous administration of this drug has been introduced with similar therapeutic response rates in patients with MM [26].

Some drugs can cause thrombotic microangiopathy (TMA) [27], and drug-induced TMA can be observed in patients receiving agents that are used in the management of TTP such as CSA [17]. As an agent recently introduced in the setting of relapsed/refractory TTP, although rare, bortezomib was also shown to be associated with drug-induced TMA in patients with MM [28–31]. Most recently, Yui et al. [32] published a paper, in which the authors shared their experience regarding PI-associated TMA in patients with MM. They retrospectively evaluated 11 patients (8 patients with carfilzomib and three with bortezomib) who developed drug-induced TMA during PI therapy in an international multicenter retrospective study.

Bortezomib in patients with relapsed/refractory acquired TTP

In the last few years, bortezomib was shown to be a new promising agent for treating patients with refractory TTP [3], and there is some data accumulated up to date. So far, there are six case reports [4–9] and a recently published case series [10], making a total number of 12 patients, demonstrating the utility of bortezomib in the treatment of relapsed/refractory TTP, which were summarized in Table 1.

In three patients [5, 6, 9], bortezomib was administered due to relapsed TTP, but in rest of the patients [4, 7, 8, 10], it was given for refractory disease. All patients had very low—even undetectable ADAMTS13 activities with high inhibitor titers (Table 1). TPE and rituximab were administered prior to bortezomib in all cases, and six of them continued receiving rituximab during bortezomib therapy. The various treatment modalities prior to and during bortezomib were displayed in Table 1.

Dose, dosing schedule, number of courses, and administration route

In almost all publications, the daily dose of bortezomib was 1.3 mg/m^2 [4–9] as indicated in patients with MM, but in the case series published by Patriquin et al. [10], bortezomib was given with a dose of 1 mg/m^2 per day.

Bortezomib was administered on days 1, 4, 8, and 11 with a total number of four doses completing one course of treatment in two patients [4, 7], and it was given with the same dosing schedule for 2 cycles in three cases [6, 8, 9]. In the report published by Yates and colleagues [5], the presented patient received bortezomib on days 1 and 8 of a 21-day cycle completing six courses and an additional dose, which makes a total of 13 administrations. In the case series by Patriquin et al. [10], two patients received three doses, two cases got two doses, and the remaining two received only one dose of bortezomib, and none of the patients completed the classical twice-weekly dosing schedule.

In three reports [4, 6, 7], the administration route of bortezomib was not given, and bortezomib was given subcutaneously in the case displayed by Yates et al. [5]. In one patient [8], four doses of bortezomib were administered subcutaneously, but another four doses were given intravenously due to insufficient response to prior subcutaneous administration. In the most recent report, five patients received subcutaneous bortezomib, and the remaining one had this drug intravenously [10]. Also Acedillo and colleagues

Table 1 Published cases with relapsed/refractory TTP who received bortezomib

Author, year of publication, reference	Number of patients treated, *n*	Median age, years (range)	Gender (F/M)	Previous episodes of TTP, *n*	ADAMTS13 activity (%)/inhibitor titer (BU)	Therapy(ies) prior to bortezomib administration	Therapy(ies) during bortezomib treatment	Median number of bortezomib administrations, *n* (range)	Dose of bortezomib, mg/m^2 per day	Route of bortezomib administration	Any toxicity(ies) associated with bortezomib treatment	Follow-up period off-therapy, days	Outcome (alive/dead)
Shortt et al., 2013, [4]	1	53	1/0	None	<3/3.2	TPE PRED HD-MP CY RTX NAC	TPE RTX NAC	4	1.3	NR	NR	60	1/0
Yates et al., 2014, [5]	1	48	1/0	7	<5/0.4–0.6	TPE RTX PRED CY	TPE	13	1.3	SC	Pulmonary toxicity	169	1/0
Mazepa et al., 2014, [6]	1	51	1/0	2	0/3.0	TPE PRED RTX SPL VCR MMF	TPE PRED MMF CY	8	1.3	NR	NR	120	1/0
van Balen et al., 2014, [7]	1	16	1/0	None	<1/positive[a]	FFP TPE PRED RTX	TPE PRED RTX	4	1.3	NR	NR	150	1/0
Patel et al., 2016, [8]	1	22	1/0	None	<5/2.4	TPE HD-MP RTX	TPE	4 4	1.3 1.3	SC IV	Grade 1 PN	540	1/0
Acedillo et al., 2016, [9]	1	36	0/1	1	<1/49	TPE MP RTX CSA	SPL MP NAC CY RTX	8	1.3	IV	Intra-abdominal abscess Central line bacteremia Left empyema	365	1/0
Patriquin et al., 2016, [10]	6	52.5 (27–76)	3/3	None	<5–10/high[b]	TPE HD-MP RTX MMF NAC	TPE RTX PRED	2 (1–3)	1	5 SC/1 IV	Cardiac toxicity	NR	5/1

CSA cyclosporine A, *CY* cyclophosphamide, *F* female, *FFP* fresh frozen plasma, *HD-MP* high-dose methylprednisolone, *IV* intravenous, *M* male, *MMF* mycophenolate mofetil, *NAC* n-acetyl cysteine, *NR* not reported, *PN* peripheral neuropathy, *PRED* prednisone, *SC* subcutaneous, *SPL* splenectomy, *TPE* therapeutic plasma exchange, *VCR* vincristine

[a] The antibody titer of the patient described in reference #7 was not quantified, but only stated as positive

[b] All patients had high levels of ADAMTS13 antibody, but the inhibitor titers were measured using different assays

administered bortezomib intravenously completing two courses of therapy [9].

Efficacy and outcome

Among the 12 cases with relapsed/refractory acquired TTP published in the literature, 11 of them survived the acute episode, but one died due to cardiac arrest [10]. All of the survivors quit receiving TPE with a clinical remission, and improvements were observed in antibody concentrations. The survival data were available in six reports [4–9], and after a median follow-up of 160 days (range, 60–540 days), none of the survivors relapsed (Table 1).

Toxicity

The bortezomib treatment was generally well tolerated, with no AEs reported in three reports [4, 6, 7]. In one patient with underlying interstitial lung disease, bortezomib was discontinued after 13 doses due to worsening the pulmonary function, which was attributed to bortezomib-associated pulmonary toxicity [5]. In another case published by Patel et al. [8], the patient experienced grade 1 neuropathy of the hands and feet after intravenously bortezomib, which spontaneously resolved in 2 months (Table 1). In the paper by Patriquin and colleagues [10], where patients received relatively low daily doses of bortezomib with less number of administrations compared to other cases published in the literature, five patients did not have any AEs after bortezomib treatment, but one patient died after one dose of bortezomib due to cardiac complication. However, that patient already had evidence of myocardial injury most probably due to TTP prior to that single bortezomib administration, so it is hard to attribute this complication to bortezomib, knowing the fact that bortezomib-associated cardiotoxicity is usually observed in patients with higher cumulative doses or preceding cardiovascular risk factors [33]. In the case described by Acedillo et al. [9], the patient had experienced infectious complications; however, the patient had received multiple lines of treatment prior to and during bortezomib administration including splenectomy (Table 1).

None of the patients experienced any signs of drug-induced TMA after they were exposed to bortezomib.

The rationale of bortezomib use and mechanism of action

Rituximab is a monoclonal antibody, which targets the CD20 antigen found on B cell surfaces. Although rituximab effectively destroys B cells expressing CD20 markers, plasma cells do not express this antigen, and the source of immunoglobulin G autoantibodies against ADAMTS13 includes both mature B cells and plasma cells.

Bortezomib functions through the selective inhibition of proteasomes, leading to cell cycle arrest and apoptosis of the plasma cells. So in patients who remain refractory to rituximab administration, it would be beneficial to use bortezomib, because in addition to CD20+ B cell depletion that had already been accomplished by rituximab, bortezomib might eliminate the plasma cells, which most probably produce the remaining autoantibodies against ADAMTS13 [4]. Bortezomib also induces apoptosis and inhibits maturation in dendritic cells, which was shown to be a possible alternative mechanism of action for its beneficial effects in patients with relapsed/refractory TTP [34, 35].

Bortezomib maintenance in the setting of relapsed/refractory TTP

As an effective agent in treating patients with relapsed or refractory TTP, rituximab was also shown to be beneficial at least in some patients with chronic relapsing TTP when used as a maintenance therapy inducing durable clinical and laboratory remissions [36]. Also in patients who clinically recovered from a TTP episode and had persistent severe acquired ADAMTS13 deficiency during the follow-up, preemptive rituximab administration can be considered in order to prevent relapses [37]. In addition to rituximab, CSA can be used effectively in this setting, and it can be administered without major AEs for relatively longer durations [17].

Bortezomib-based maintenance therapy has been assessed previously in patients with MM with a progression-free survival benefit [38]. The safety profile of bortezomib was acceptable, although nearly half of the patients were able to complete the planned 2 years of intravenous bortezomib maintenance therapy partly due to neurotoxicity. Since the subcutaneous administration of bortezomib is usually efficient and safe, although there is no current evidence available regarding this way of use, maybe in the near future bortezomib can be used as a maintenance therapy in some patients with chronic relapsing TTP.

Conclusion

Although TPE with corticosteroids usually induce clinical and laboratory remissions in patients with TTP, some patients remain resistant to this therapy approach or relapse after an initial response. In the current daily practice, rituximab among some other alternatives can be safely used in those patients; however, there are still some percent of patients who remain refractory to those treatment modalities. Recently, among these multi-treatment refractory patients, bortezomib was introduced to be beneficial, without any serious AEs, although the number of patients who were treated with this drug is still

limited. In most of the patients displayed in the literature, many other treatment modalities were administered prior to and/or during bortezomib administration, so the effect of proteasome inhibition alone can be difficult to dissect, and possible publication bias may be operating, mainly due to overrepresentation of positive literature in small series. To conclude, bortezomib can be an alternative treatment option in patients with relapsed/refractory TTP, but prospective trials are needed to determine the dosing, administration route, the treatment schedule, and the role of maintenance with this treatment.

Compliance with ethical standards

Conflict of ınterest AEE has received honorarium from Roche.

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