Clinical Policy Bulletin:
Bortezomib (Velcade)

Number: 0675

Policy

Aetna considers bortezomib (Velcade) for intravenous or subcutaneous administration medically necessary for treatment of the following indications:

- Adult T-cell leukemia/lymphoma
- Mantle cell lymphoma
- Multicentric Castleman’s disease, as subsequent therapy with or without rituximab for disease that has progressed following treatment of relapsed/refractory or progressive disease
- Multiple myeloma
- Mycosis fungoides/Sezary syndrome
- Primary cutaneous anaplastic large cell lymphoma (ALCL) with multifocal lesions and cutaneous ALCL with regional nodes (excludes systemic ALCL)
- Progressive solitary plasmacytoma
- Second-line treatment of persons with relapsed or refractory angioimmunoblastic T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, anaplastic large cell lymphoma, or enteropathy-associated T-cell lymphoma who are not candidates for high-dose chemotherapy and autologous stem cell transplantation
- Second-line therapy for primary cutaneous marginal zone or follicle center lymphoma
- Systemic light-chain amyloidosis
- Waldenstrom’s macroglobulinemia/lymphoplasmacytic lymphoma

Aetna considers bortezomib experimental and investigational for all other indications, including the following because its effectiveness for these indications has not been established:

- As monotherapy or in combination with other chemotherapeutics for the treatment of other hematological malignancies (e.g., chronic lymphocytic leukemia, chronic myeloid leukemia, diffuse large B-cell lymphoma, follicular lymphoma, Hodgkin’s disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and myelodysplasia), solid tumors (e.g., biliary tract cancer, breast cancer, colon cancer, head and neck cancer, metastatic melanoma (lung), non-small cell lung cancer, ovarian cancer, pancreatic cancer, renal carcinoma, and androgen-dependent prostate cancer), neuroendocrine tumors (e.g., carcinoid or islet cell tumors), or sarcoma (including osteosarcoma)
- Autoimmune disorders including autoimmune hemolytic anemia and autoimmunity in children
- Follicular lymphoma
- Gastric MALT lymphoma
- Hepatocellular carcinoma
- Histiocytic sarcoma.
- HIV infection and immunological/inflammatory conditions (e.g., arthritis, asthma, multiple sclerosis, and reperfusion injury)
Hyper IgG4 syndrome
Kidney transplant rejection, liver transplant rejection, and other antibody-mediated rejection
Myasthenia gravis
Non-gastric MALT lymphoma
Post-transplant lymphoproliferative disorder
Splenic marginal zone lymphoma
Systemic ALCL

See also CPB 0404 - Interferons, CPB 0497 - Hematopoietic Cell Transplantation for Multiple Myeloma, CPB 0524 - Zoledronic Acid, CPB 0634 - Non-myeloablative Bone Marrow/Peripheral Stem Cell Transplantation (Mini-Allograft / Reduced Intensity Conditioning Transplant), and CPB 0672 - Pamidronate (Aredia).

Background

The proteasome, a multi-catalytic protease present in all eukaryotic cells, plays an important role in the regulation of cell cycle, neoplastic growth, and metastasis. Proteasome inhibitors specifically induce apoptosis in cancer cells, but most proteasome inhibitors are not suitable for clinical development. Velcade (bortezomib), a specific, selective inhibitor of the 26S proteasome, is a novel dipeptide boronic acid that is the first proteasome inhibitor to have progressed to clinical trials. A unique feature of bortezomib involves the inhibition of nuclear factor (NF)-kappaB activation through stabilization of the inhibitor protein IkappaB. Pre-clinical studies have demonstrated that through the prevention of IkappaB degradation, bortezomib may block chemotherapy-induced NF-kappaB activation and augment the apoptotic response to chemotherapeutic agents. NF-kappaB is a transcription factor that increases the production of growth factors (e.g., interleukin-6), cell-adhesion molecules, and anti-apoptotic factors, all of which contribute to the growth of the tumor cell and/or protection from apoptosis. In addition, bortezomib appears to enhance the stabilization of p21 and p27, as well as transcription factor p53.

In pre-clinical models of breast, lung, pancreatic, and ovarian tumor types, bortezomib inhibited tumor growth and showed anti-angiogenic properties. Bortezomib exhibited the greatest activity when combined with standard chemotherapeutic agents, such as irinotecan, gemcitabine, and docetaxel, suggesting its potential additive/synergistic role in overcoming resistance to conventional chemotherapy. Evidence from early clinical trials suggested that bortezomib can be given at pharmacologically active doses in combination with standard doses of chemotherapy with manageable toxicities. Responses have been seen and no evidence of additive toxicity has been exhibited in combination agent trials.

Bortezomib was initially approved as a third-line treatment of relapsed and refractory multiple myeloma (MM) by the Food and Drug Administration (FDA) under the accelerated approval program. The FDA evaluated the safety and effectiveness of bortezomib based on a study of 202 patients with relapsed and refractory MM who had received at least 2 prior therapies and showed disease progression on their most recent therapy (the SUMMIT trial). Bortezomib was administered intravenously at 1.3 mg/m2/dose twice-weekly for 2 weeks, followed by a 10-day rest period (21-day treatment cycle) for a maximum of 8 treatment cycles. In the study population, the median number of previous therapies was 6, and 64 % of patients had received stem cell transplant or other high dose therapy. Results (Blade criteria -- a rigorous assessment standard used to describe changes in disease status, including a confirmation 6 weeks later) in the 188 eligible and evaluable subjects included complete response (CR) in 5 patients, for a CR rate of 2.7 % (95 confidence interval [CI]: 1 % to 6 %); partial responses (PR) occurred in 47 patients for a PR rate of 25 % (95 CI: 19 % to 32 %). Clinical remissions by SWOG criteria were observed in 17.6 % of patients (95 % CI: 12 % to 24 %). The response lasted a median time of 1 year.

Another trial in 54 subjects with relapsed MM (the CREST trial) showed similar responses. Patients were randomized to receive either 1.0 mg/m2 or 1.3 mg/m2 of bortezomib for Injection therapy for up to 24 weeks (days 1, 4, 8 and 11 of a 21-day cycle, for up to 8 cycles). For patients in the 1.3 mg/m2 treatment group, the overall response (defined as the combined total of complete and partial
remissions and minimal responses) was 69%. For patients in the 1.0 mg/m² treatment group, the overall response was 59%. The overall median time to progression was 11 months.

The FDA approved a supplemental New Drug Application (sNDA) for Velcade, which expands the label to include the treatment of patients with MM who have received at least 1 prior therapy. The approval was based on data from the randomized phase III APEX study that compared single-agent bortezomib to high-dose dexamethasone in 669 patients with relapsed MM who had received 1 to 3 prior therapies (Richardson et al, 2005). The study demonstrated a significant survival advantage with bortezomib in patients with MM who had received 1 to 3 prior therapies. The combined complete and partial response rates were 38% for bortezomib and 18% for dexamethasone (p < 0.001), and the complete response rates were 6% and less than 1%, respectively (p < 0.001). Median times to progression in the bortezomib and dexamethasone groups were 6.22 months (189 days) and 3.49 months (106 days), respectively (hazard ratio, 0.55; p < 0.001). The 1-year survival rate was 80% among patients taking bortezomib and 66% among patients taking dexamethasone (p = 0.003), and the hazard ratio for overall survival with bortezomib was 0.57 (p = 0.001). Grade 3 or 4 adverse events were reported in 75% of patients treated with bortezomib and in 60% of those treated with dexamethasone.

Guidelines from the National Comprehensive Cancer Network (NCCN, 2007) also recommend use of bortezomib for induction chemotherapy as a primary treatment for progressive solitary plasmacytoma or smoldering myeloma.

Mantle cell lymphoma (MCL) is a lymphoma that is refractory to most current chemotherapy regimens. Several clinical studies have demonstrated that bortezomib has clinical effects on MCL. Lenz et al (2004) stated that new therapeutic strategies such as radioactively labeled antibodies or molecular targeting agents (e.g. bortezomib or flavopiridol) are urgently warranted to further improve the clinical outcome of MCL. The NCCN guidelines (2004) also recommend bortezomib as a second-line treatment of MCL. According to the NCCN, first line treatment of mantle cell lymphoma includes rituximab plus combination chemotherapy (e.g., hyperCVAD, CHOP, EPOCH).

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of generally aggressive neoplasms, which constitute less than 15% of all non-Hodgkin's lymphomas (NHLs) in adults. For the myriad forms of aggressive peripheral T-cell lymphomas, treatment approaches similar to those used for B-cell lymphomas have been used for patients with either localized or advanced stage disease, with autologous hematopoietic cell transplantation utilized in selected patients. Phase II studies of bortezomib showed encouraging results in B-cell lymphomas (Goy, 2005; O'Connor, 2005).

NCCN guidelines (2012) recommend use of bortezomib as second-line therapy for relapsed or refractory angioimmunoblastic T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, anaplastic large cell lymphoma, or enteropathy-associated T-cell lymphoma in noncandidates for transplant.

Bortezomib is administered intravenously (bolus) at a dose of 1.3 mg/m² twice a week for 2 weeks, followed by a 10-day rest period. At least 3 days should elapse between consecutive doses of bortezomib. The most common side effects associated with bortezomib include nausea, fatigue, diarrhea, constipation, headache, decreased appetite, decreased platelets and red blood cells, fever, vomiting, and peripheral neuropathy (numbness and tingling, and occasionally pain in the extremities). Bortezomib should be interrupted for any grade-3 non-hematological (excluding neuropathy) or grade-4 hematological toxicity.

In a phase II clinical trial (n = 27), Markovic et al (2005) reported that single-agent bortezomib, administered twice-weekly for 2 of every 3 weeks at a dose of 1.5 mg/m², was not found to be effective in the treatment of patients with metastatic melanoma.

In a multi-center phase II study (n = 21), Maki et al (2005) stated that bortezomib has minimal activity in soft tissue sarcoma as a single agent. These researchers concluded that if studied further in sarcomas, bortezomib should be investigated in combination with agents with demonstrated pre-clinical synergy. In another phase II clinical (n = 16), Shah et al (2005) found that despite achieving the surrogate biologic end point, single-agent bortezomib did not induce any objective responses in patients with metastatic carcinoid or islet cell tumors.
Dimopoulos et al (2005) noted that bortezomib is a selective proteasome inhibitor which has shown significant activity in a variety of hematologic malignancies including multiple myeloma, mantle cell lymphoma and marginal zone lymphoma. Thus, this agent is worth studying in patients with Waldenstrom's macroglobulinemia (WM). Patients with refractory or relapsed WM were treated with bortezomib administered intravenously at a dose of 1.3 mg/m² on days 1, 4, 8 and 11 in a 21-day cycle for a total of 4 cycles. A total of 10 previously treated patients with WM were treated with bortezomib. Most patients had been exposed to all active agents for WM and 8 patients had received 3 or more regimens. Six of these patients achieved a partial response which occurred at a median of 1 month. The median time to progression in the responding patients is expected to exceed 11 months. Bortezomib was relatively well-tolerated. The more common toxicities were mild or moderate thrombocytopenia, fever and fatigue while peripheral neuropathy occurred in 3 patients and 1 patient developed severe paralytic ileus. The authors concluded that these preliminary data indicated that bortezomib is an active agent in patients with heavily pretreated relapsed/refractory WM. Four cycles of this agent may be adequate to assess sensitivity in this disease. They noted that further studies are needed to confirm their results and to evaluate combinations of bortezomib with other active agents.

In a phase II clinical study, Chen et al (2007) evaluated the effectiveness and toxicity of single-agent bortezomib in WM. Symptomatic patients, untreated or previously treated, received bortezomib 1.3 mg/m² intravenously days 1, 4, 8, and 11 on a 21-day cycle until 2 cycles past complete response (CR), stable disease (SD) attained, progression (PD), or unacceptable toxicity. Responses were based on both para-protein levels and bi-dimensional disease measurements. A total of 27 patients were enrolled. A median of 6 cycles (range of 2 to 39) of bortezomib were administered. Twenty-one patients had a decrease in immunoglobulin M (IgM) of at least 25 %, with 12 patients (44 %) reaching at least 50 % IgM reduction. Using both IgM and bi-dimensional criteria, responses included 7 partial responses (PRs; 26 %), 19 SDs (70 %), and 1 PD (4 %). Total response rate was 26 %. IgM reductions were prompt, with nodal responses lagging. Hemoglobin levels increased by at least 10 g/L in 18 patients (66 %). Most non-hematological toxicities were grade 1 to 2, but 20 patients (74 %) developed new or worsening peripheral neuropathy (5 patients with grade 3, no grade 4), a common cause for dose reduction. Onset of neuropathy was within 2 to 4 cycles and reversible in the majority. Hematological toxicities included grade 3 to 4 thrombocytopenia in 8 patients (29.6 %) and neutropenia in 5 (19 %). Toxicity led to treatment discontinuation in 12 patients (44 %), most commonly because of neuropathy. The authors concluded that bortezomib is effective in WM, but neurotoxicity can be dose limiting. The slower response in nodal disease may require prolonged therapy, perhaps with a less intensive dosing schedule to avoid early discontinuation because of toxicity. They stated that future studies of bortezomib in combination with other agents are warranted. Furthermore, Vijay and Gertz (2007) noted that novel agents such as bortezomib, perifosine, atacicept, oblimersen sodium, and tositumomab show promise as rational targeted therapy for WM.

The published evidence for bortezomib in large B-cell lymphoma is limited to small uncontrolled studies. Current guidelines from the NCCN (2008) and the National Cancer Institute (NCI, 2008) do not state that bortezomib is effective for diffuse large B-cell lymphoma (DLBCL). Evidence-based guidelines from Cancer Care Ontario (Reece et al, 2006) reviewed the evidence for bortezomib in DLBCL and other NHLs; the guidelines stated that there is insufficient evidence to support the use of bortezomib outside of clinical trials in patients with NHL.

There is limited published evidence for the use of bortezomib for systemic light chain amyloidosis, consisting of 1 phase II clinical study (Kastritis et al, 2007), small case series (Wechalekar et al, 2008), and case reports (Borde et al, 2008). NCCN's Drug and Biologics Compendium (2008) lists systemic light chain amyloidosis as an indication for bortezomib. However, NCCN guidelines (2009) indicate that this and other treatments for systemic light chain amyloidosis should be provided in the context of a clinical trial.

Kastritis et al (2007) assessed the activity and feasibility of the combination of bortezomib and dexamethasone (BD) in patients with AL amyloidosis. A total of 18 patients, including 7 who had relapsed or progressed after previous therapies were treated with BD; 11 (61 %) patients had 2 or more organs involved; kidneys and heart were affected in 14 and 15 patients, respectively. The
majority of patients had impaired performance status and high brain natriuretic peptide values; serum creatinine was elevated in 6 patients. Among evaluable patients, 94 % had a hematological response and 44 % a hematological complete response, including all 5 patients who had not responded to prior high dose dexamethasone-based treatment and 1 patient under dialysis. Five patients (28 %) had a response in at least 1 affected organ. Hematological responses were rapid (median of 0.9 months) and median time to organ response was 4 months. Neurotoxicity, fatigue, peripheral edema, constipation and exacerbation of postural hypotension were manageable although necessitated dose adjustment or treatment discontinuation in 11 patients. The authors concluded that the combination of BD is feasible in patients with AL amyloidosis. Patients achieve a rapid hematological response and toxicity can be managed with close follow-up and appropriate dose adjustment. This treatment may be a valid option for patients with severe heart or kidney impairment.

Wechalekar et al (2008) reported preliminary observations on the effectiveness of bortezomib in 20 patients with primary amyloidosis (AL) whose clonal disease was active despite treatment with a median of 3 lines of prior chemotherapy, including a thalidomide combination in all cases. Patients received a median of 3 (range of 1 to 6) cycles of bortezomib and 9 (45 %) patients received concurrent dexamethasone. Three (15 %) patients achieved complete hematological responses, and a further 13 (65 %) achieved partial responses. Fifteen (75 %) patients experienced some degree of toxicity, which in 8 (40 %) cases resulted in discontinuation of bortezomib. The authors stated that bortezomib shows promise in the treatment of systemic AL amyloidosis.

Guidelines from the NCCN indicates bortezomib as a single agent for primary treatment of symptomatic hyperviscosity in WM. Treon et al (2007) reported on an uncontrolled clinical study which found bortezomib as an active agent in relapsed or refractory WM. In this study, 27 patients with WM received up to 8 cycles of bortezomib. All but 1 patient had relapsed/or refractory disease. Following therapy, median serum IgM levels declined from 4,660 to 2,092 mg/dL (p < 0.0001). The overall response rate was 85 %, with 10 and 13 patients achieving minor and major responses, respectively. The investigators reported that responses were prompt and occurred at median of 1.4 months. The median time to progression for all responding patients was 7.9 months. The most common grade III/IV toxicities were sensory neuropathies (22.2 %), leukopenia (18.5 %), neutropenia (14.8 %), dizziness (11.1 %), and thrombocytopenia (7.4 %). The investigators observed that sensory neuropathies resolved or improved in nearly all patients following cessation of therapy.

Chen and colleagues (2007) also found bortezomib an active agent in WM. In an uncontrolled clinical trial, symptomatic patients with WM (n = 27), untreated or previously treated, received bortezomib on a 21-day cycle until 2 cycles past complete response (CR), stable disease (SD), attained, progression (PD), or unacceptable toxicity. A median of 6 cycles (range of 2 to 39) of bortezomib were administered. The investigators reported that 21 patients had a decrease in immunoglobulin M (IgM) of at least 25 %, with 12 patients (44 %) reaching at least 50 % IgM reduction. Using both IgM and bidimensional criteria, responses included 7 partial responses (PRs; 26 %), 19 SDs (70 %), and 1 PD (4 %). Total response rate was 26 %. The investigators reported that IgM reductions were prompt, with nodal responses lagging. Hemoglobin levels increased by at least 10 g/L in 18 patients (66%). The investigators observed that most non-hematologic toxicities were grade 1 to 2, but 20 patients (74 %) developed new or worsening peripheral neuropathy (5 patients with grade 3, no grade 4), a common cause for dose reduction. Onset of neuropathy was within 2 to 4 cycles and reversible in the majority. Hematologic toxicities included grade 3 to 4 thrombocytopenia in 8 patients (29.6 %) and neutropenia in 5 (19 %). Toxicity led to treatment discontinuation in 12 patients (44 %), most commonly because of neuropathy.

Eom and associates (2009) performed a retrospective analysis of 69 patients with MM who received bortezomib-containing regimens (n = 30) or vincristine, doxorubicin and dexamethasone (VAD; n = 39) before collection of peripheral blood stem cells and autologous stem cell transplantation (ASCT). Objective response rate (at least a partial response) prior to ASCT was documented in 27 (90 %) of 30 and 31 (81.6 %) of evaluable 38 patients with bortezomib-containing regimens and VAD, respectively. The difference between the 2 groups was not significant (p = 0.494). However, the high-quality response rate with very good partial response (VGPR) or more in the bortezomib group was significantly higher compared with the VAD group (66.7 % versus 34.2 %, respectively, p = 0.002).
The superiority of bortezomib-containing regimens in the high-quality response rate remained significant for only the newly diagnosed patients (n = 16, p = 0.008). The engraftment data as well as stem cell harvesting were comparable between the 2 groups. The major bortezomib-related toxicities were thrombocytopenias and peripheral neuropathies; toxicities of VAD were hematologic and infectious. After ASCT, the difference between the 2 groups did not reach the level of statistical significance with respect to progression-free survival (PFS) and overall survival (OS) (p = 0.498 and 0.835, respectively). The authors concluded that the results of this retrospective comparison of bortezomib-containing regimens with the VAD as induction treatment prior to ASCT for MM provided a demonstration of the superiority of bortezomib therapy in terms of achieving a high-quality response. However, survivals following ASCT did not differ according to the induction regimens.

In a single institution, phase II study, Uy and colleagues (2009) examined the role of bortezomib as induction therapy before ASCT and its role as maintenance therapy after ASCT for patients with MM. A total of 40 patients were given bortezomib sequentially pre-ASCT and as maintenance therapy post ASCT. Pre-transplant bortezomib was administered for 2 cycles followed by high-dose melphalan 200 mg/m(2) with ASCT of granulocyte colony stimulating factor-mobilized peripheral blood mononuclear cells. Post-transplant bortezomib was administered weekly for 5 out of 6 weeks for 6 cycles. No adverse effects were observed on stem cell mobilization or engraftment. An overall response rate of 83 % with a complete response + VGPR of 50 % was observed with this approach. Three-year Kaplan-Meier estimates of disease-free survival and OS were 38.2 % and 63.1 %, respectively. Bortezomib reduced CD8(+) cytotoxic T cell and CD56(+) natural killer cell peripheral blood lymphocytes subsets and was clinically associated with high rates of viral reactivation to varicella zoster. The authors stated that interpretation of the role of bortezomib maintenance in myeloma based on this single study is limited because of the relatively small sample size and relatively short duration of maintenance therapy. They noted that larger prospective randomized studies of post transplant bortezomib are needed and are currently ongoing.

Perry et al (2009) noted that antibody production by normal plasma cells (PCs) against human leukocyte antigens (HLA) can be a major barrier to successful transplantation. These investigators tested 4 reagents with possible activity against PCs (rituximab, polyclonal rabbit anti-thymocyte globulin (rATG), intravenous immunoglobulin (IVIG) and bortezomib) to determine their ability to cause apoptosis of human bone marrow-derived PCs and subsequently block IgG secretion in vitro. Rituximab, IVIG, and rATG all failed to cause apoptosis of PCs and neither rituximab nor rATG blocked antibody production. In contrast, bortezomib treatment led to PC apoptosis and thereby blocked anti-HLA and anti-tetanus IgG secretion in vitro. Two patients treated with bortezomib for humoral rejection after allogeneic kidney transplantation demonstrated a transient decrease in bone marrow PCs in vivo and persistent alterations in allo-antibody specificities. Total IgG levels were unchanged. The authors concluded that proteasome activity is important for PC longevity and its inhibition may lead to new techniques of controlling antibody production in vivo.

Everly et al (2009) described the biochemistry and physiology of proteasome inhibition and discussed recent studies with proteasome inhibitor therapy in organ transplantation. Traditional anti-humoral therapies do not deplete PCs. Proteasome inhibition depletes both transformed and non-transformed PCs in animal models and human transplant recipients. Bortezomib is a first in a class proteasome inhibitor that has been shown to effectively treat antibody-mediated rejection in kidney transplant recipients. In this experience, bortezomib provided reversal of histological changes and also induced a reduction in donor-specific anti-HLA antibody levels. Recent experiences have also shown that bortezomib reduces donor-specific anti-HLA antibody in the absence of rejection. Finally, evidence has been presented that bortezomib therapy depletes HLA-specific antibody producing PCs. The authors concluded that proteasome inhibition induces a complex series of biochemical events that results in pleiotropic effects on multiple cell populations, and PCs in particular. Initial clinical results have provided evidence that bortezomib effectively treats antibody-mediated rejection and acute cellular rejection and reduces or eliminates donor-specific anti-HLA antibody. They stated that carefully designed clinical trials are needed to accurately define the role of proteasome inhibition in transplant recipients.

Shapovalov et al (2010) hypothesized that proteasome inhibition will induce Runx2 and Runx2-dependent Bax expression sensitizing osteosarcoma cells to apoptosis. These researchers had
shown that bortezomib increased Runx2 and Bax in osteosarcoma cells. In vitro, bortezomib suppressed growth and induced apoptosis in osteosarcoma cells but not in non-malignant osteoblasts. Experiments involving intra-tibial tumor xenografts in nude mice showed significant tumor regression in bortezomib-treated animals. Immunohistochemical studies revealed that bortezomib inhibited cell proliferation and induced apoptosis in osteosarcoma xenografts. These effects correlated with increased immunoreactivity for Runx2 and Bax. The authors concluded that these findings indicate that bortezomib suppresses growth and induces apoptosis in osteosarcoma in vitro and in vivo suggesting that proteasome inhibition may be effective as an adjuvant to current treatment regimens for these tumors.

Stegall and Gloor (2010) described recent studies regarding the mechanisms of antibody-mediated rejection (AMR) and new clinical protocols aimed at prevention and/or treatment of this difficult clinical entity. These investigators noted that the natural history of acute AMR after positive cross-match kidney transplantation involves an acute rise in donor-specific alloantibody (DSA) in the first few weeks following transplantation. Whereas the exact cellular mechanisms responsible for AMR are not known, it seems likely that both pre-existing plasma cells and the conversion of memory B cells to new plasma cells play a role in the increased DSA production. One recent study suggested that combination therapy with plasmapheresis, high-dose IVIG and rituximab was more effective treatment for AMR than high-dose IVIG alone, but the role of anti-CD20 antibody is still unclear. Two new promising approaches to AMR focus on depletion of plasma cells with bortezomib as well as the inhibition of terminal complement activation with eculizumab. The authors concluded that the pathogenesis of AMR in several different clinical settings is becoming clearer and more effective treatments are being developed. Whether the prevention or successful treatment of AMR will decrease the prevalence of chronic injury and improved long-term graft survival will require longer-term studies.

Wiedmann and Mossner (2010) noted that carcinoma of the biliary tree are rare tumors of the gastrointestinal tract with worldwide rising incidence for intra-hepatic cholangiocarcinoma during the last years. Although complete surgical resection is the only curative approach, this can be accomplished in a minority of patients, since most of them present with advanced disease. In addition, those patients who have undergone complete surgical resection experience a high tumor recurrence rate. Non-resectable biliary tract cancer is associated with a poor prognosis due to wide resistance to chemotherapeutic agents and radiotherapy. It is therefore essential to search for new therapeutic approaches. After several years of pre-clinical research, the first clinical study data are now available for this tumor entity. Inhibitors of the EGFR family, such as erlotinib, cetuximab, and lapatinib were recently investigated. In addition, bortezomib, an inhibitor of the proteasome, imatinib mesylate, an inhibitor of c-kit-R, bevacizumab, an inhibitor of vascular endothelial growth factor (VEGF), and sorafenib (BAY 43-9006), a multiple kinase inhibitor that blocks not only receptor tyrosine kinases but also serine/threonine kinases along the RAS/RAF/MEK/ERK pathway, were studied, as well. Although early evidence of anti-tumor activity was seen, the results are still preliminary and require further investigations.

Follicular lymphoma (FL) is classified as a non-Hodgkin's lymphoma. It is an indolent (slow-growing) cancer that affects B-cell lymphocytes. In a phase II clinical trial, Di Bella et al (2010) evaluated the safety and effectiveness of single-agent bortezomib in indolent B-cell lymphoma that had relapsed from or was refractory to rituximab. A total of 60 y patients were enrolled: 59 were treated with bortezomib 1.3 mg/m(2) on days 1, 4, 8, and 11 for up to 8 21-day cycles; responders could receive 4 additional cycles; maintenance was optional. Fifty-three evaluable patients completed more than 2 cycles. The median age was 70 years, 53 % female, Ann Arbor stage III-IIE (28 %) and IV (65 %); 43 patients (72 %) had more than 2 prior regimens; and 6 patients went on to maintenance. Overall responses are as follows: 1 complete response (1.9 %), 3 unconfirmed complete response (5.7 %), 3 partial response (5.7 %), 34 stable disease (64.2 %), and 12 progressive disease (22.6 %). Median time to response = 2.2 months (range of 1.2 to 5.3 months); duration of response = 7.9 months (2.8 to 21.3 months); 1-year survival was 73 % and 2-year survival was 58 %; median survival = 27.7 months (range of 1.4 to 30.9 months); median progression-free survival = 5.1 months; median event-free survival = 1.8 months (range of 0.2 to 27.7 months). Treatment-related grade 3 or 4 adverse events included: thrombocytopenia (20 %), fatigue (10 %), neutropenia (8.5 %), and neuropathy and diarrhea (6.8 % each). The authors concluded that these findings showed that
bortezomib has modest activity against marginal zone and FL; it has the potential for combination with other agents in low-grade lymphomas. Maintenance therapy should be explored further.

Leonard and Martin (2010) stated that unlabeled and radiolabeled anti-CD20 monoclonal antibodies have had a significant impact in the care of patients with FL over the past decade. More recently, bendamustine has demonstrated activity in refractory FL, and has been explored as initial therapy and in novel combinations. Whereas outcomes for this patient population have significantly improved, there remains substantial unmet need for patients who require more effective and better-tolerated therapies. Novel anti-CD20 antibodies and other immunotherapies against different B-cell antigens are under active investigation. The proteosome inhibitor bortezomib and the immunomodulatory agent lenalidomide have demonstrated single-agent activity and are currently in randomized trials. Other novel compounds have demonstrated activity in broad-based clinical studies in B-cell malignancies. However, considerable challenges remain in efficiently demonstrating which patient subsets can benefit from these novel compounds and which combinations may have the greatest clinical benefit in further improving outcomes for patients with FL.

In a phase III clinical trial, Coiffier et al (2011) compared the safety and effectiveness of rituximab alone or combined with bortezomib in patients with relapsed or refractory FL. Rituximab-naive or rituximab-sensitive patients aged 18 years or older with relapsed grade 1 or 2 FL were randomly assigned (1:1) to receive 5 35-day cycles consisting of intravenous infusions of rituximab 375 mg/m(2) on days 1, 8, 15, and 22 of cycle 1, and on day 1 of cycles 2 to 5, either alone or with bortezomib 1-6 mg/m(2), administered by intravenous injection on days 1, 8, 15, and 22 of all cycles. Randomization was stratified by FLIPI score, previous use of rituximab, time since last therapy, and region. Treatment assignment was based on a computer-generated randomization schedule prepared by the sponsor. Patients and treating physicians were not masked to treatment allocation. The primary endpoint was progression-free survival analyzed by intention-to-treat. A total of 676 patients were randomized to receive rituximab (n = 340) or bortezomib plus rituximab (n = 336). After a median follow-up of 33.9 months (IQR 26.4 to 39.7), median progression-free survival was 11.0 months (95 % CI: 9.1 to 12.0) in the rituximab group and 12.8 months (11.5 to 15.0) in the bortezomib plus rituximab group (hazard ratio 0.82, 95 % CI: 0.68 to 0.99; p = 0.039). The magnitude of clinical benefit was not as large as the anticipated prespecified improvement of 33 % in progression-free survival. Patients in both groups received a median of 5 treatment cycles (range of 1 to 5); 245 of 339 (72 %) and 237 of 334 (71 %) patients in the rituximab and bortezomib plus rituximab groups, respectively, completed 5 cycles. Of patients who did not complete 5 cycles, most discontinued early because of disease progression (77 [23 %] patients in the rituximab group and 56 [17 %] patients in the bortezomib plus rituximab group). Rates of adverse events of grade 3 or higher (70 [21 %] of 339 rituximab-treated patients versus 152 [46 %] of 334 bortezomib plus rituximab treated patients), and serious adverse events (37 [11 %] patients versus 59 [18 %] patients) were lower in the rituximab group than in the combination group. The most common adverse events of grade 3 or higher were neutropenia (15 [4 %] patients in the rituximab group and 37 [11 %] patients in the bortezomib plus rituximab group), infection (15 [4 %] patients and 36 [11 %] patients, respectively), diarrhoea (no patients and 25 [7 %] patients, respectively), herpes zoster (1 [less than 1 %] patient and 12 [4 %] patients, respectively), nausea or vomiting (2 [less than 1 %] patients and 10 [3 %] patients, respectively) and thrombocytopenia (2 [less than 1 %] patients and 10 [3 %] patients, respectively). No individual serious adverse event was reported by more than 3 patients in the rituximab group; in the bortezomib plus rituximab group, only pneumonia (7 patients [2 %]) and pyrexia (6 patients [2 %]) were reported in more than 5 patients. In the bortezomib plus rituximab group 57 (17 %) of 334 patients had peripheral neuropathy (including sensory, motor, and sensorimotor neuropathy), including 9 (3 %) with grade 3 or higher, compared with 3 (1 %) of 339 patients in the rituximab group (no events of grade greater than or equal to 3). No patients in the rituximab group but 3 (1 %) patients in the bortezomib plus rituximab group died of adverse events considered at least possibly related to treatment. The authors concluded that although a regimen of bortezomib plus rituximab is feasible, the improvement in progression-free survival provided by this regimen versus rituximab alone was not as great as expected.

In a phase II study, Conconi et al (2011) examined the clinical activity of bortezomib in relapsed/refractory mucosa-associated lymphoid tissue (MALT) lymphoma. A total of 32 patients with relapsed/refractory MALT lymphoma were enrolled; 31 patients received bortezomib 1.3 mg/m(2) i.v., on days 1, 4, 8, and 11, for up to 6 21-day cycles. Median age was 63 years (range of 37 to 85 years).
82 years). Median number of prior therapies was 2 (range of 1 to 4). Nine patients had Ann Arbor stage I, 7 patients had stage II, and 16 patients had stage IV. Primary lymphoma localization was the stomach in 14 patients; multiple extra-nodal sites were present in 10 patients. Among the 29 patients assessable for response, the overall response rate was 48 % [95 % CI: 29 % to 67 %], with 9 complete and 5 partial responses. Nine patients experienced stable disease and 6 had disease progression during therapy. The most relevant adverse events were fatigue, thrombocytopenia, neutropenia, and peripheral neuropathy. After a median follow-up of 24 months, the median duration of response was not reached yet. Five deaths were reported, in 2 patients due to disease progression. The authors concluded that bortezomib is active in relapsed MALT lymphomas. They stated that further investigations to identify optimal bortezomib dose, schedule, and combination regimens are needed since the frequent detection of dose-limiting peripheral neuropathy.

Fowler and associates (2011) evaluated the response rate, progression-free survival, and toxicity of the combination of bortezomib, bendamustine, and rituximab (VBR) in patients with FL whose disease was relapsed or refractory to prior treatment. Patients received 5 35-day cycles of bortezomib, bendamustine, and rituximab: bortezomib administered intravenously (IV) at a dose of 1.6 mg/m(2) on days 1, 8, 15, and 22, cycles 1 to 5; bendamustine 50, 70, or 90 mg/m(2) IV over a 60-min infusion on days 1 and 2, cycles 1 to 5; and rituximab 375 mg/m(2) on days 1, 8, 15, and 22 of cycle 1 and day 1 of subsequent cycles. Patients were assessed using the International Workshop Response Criteria, with the primary end point of 60 % complete response rate. A total of 73 patients were enrolled. During the dose-escalation phase, the maximum-tolerated dose for bendamustine was not reached; the 90 mg/m(2) dose level was expanded for the efficacy assessment, and a total of 63 patients received bendamustine 90 mg/m(2). In these 63 patients, the overall response rate was 88 % (including 53 % CR). Median duration of response was 11.7 months (95 % CI: 9.2 to 13.3). Median progression-free survival was 14.9 months (95 % CI: 11.1 to 23.7). Toxicities were manageable; myelosuppression was the main toxicity (25 % and 14 % of patients experienced grade 3 to 4 neutropenia and grade 3 to 4 thrombocytopenia, respectively). Transient grade 3 to 4 neuropathy occurred in 11 % of patients. The authors concluded that the combination of bortezomib, bendamustine, and rituximab is highly active in patients with FL who have received previous treatment. The authors noted that "despite observed efficacy, our hypothesis that VBR would predict a CR rate greater than 60 % was not met. Follow-up remains short, and continued analysis of long-term responders and late effects of treatment is ongoing .... it is possible that the efficacy observed in the current study resulted entirely from bendamustine and rituximab".

In an editorial that accompanied the afore-mentioned study, Salles (2011) stated that "but given the toxicity and economic costs of these regimens, in the absence of more convincing signals supporting their clinical activity in patients with follicular lymphoma (as opposed to other lymphoma subtypes), other therapeutic options (e.g., new antibodies, immunomodulatory agents, kinase inhibitors, and so on) may be considered higher priorities for clinical trials in the field".

In a phase II clinical study, Sehn and colleagues (2011) evaluated the safety and effectiveness of bortezomib added to rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) in previously untreated advanced-stage FL. Bortezomib (1.3 mg/m(2) days 1 and 8) was added to standard-dose R-CVP (BR-CVP) for up to 8 cycles in patients with newly diagnosed stage III/IV FL requiring therapy. Two co-primary end points, complete response rate (CR/CR unconfirmed [CRu]) and incidence of grade 3 or 4 neurotoxicity, were assessed. Between December 2006 and March 2009, a total of 94 patients were treated with BR-CVP. Median patient age was 57 years (range of 29 to 84 years), and the majority had a high (47 %) or intermediate (43 %) Follicular Lymphoma International Prognostic Index score. BR-CVP was extremely well-tolerated, with 90 % of patients completing the intended 8 cycles. No patients developed grade 4 neurotoxicity, and only 5 of 94 patients (5 %; 95 % CI: 0.8 % to 9.9 %) developed grade 3 neurotoxicity, which was largely reversible. On the basis of an intention-to-treat analysis, 46 of 94 patients (49 %; 95 % CI: 38.8 % to 59.0 %) achieved a CR/CRu, and 32 of 94 patients (34 %) achieved a partial response, for an overall response rate of 83 % (95 % CI: 75.4 % to 90.6 %). The authors concluded that addition of bortezomib to standard-dose R-CVP for advanced-stage FL is feasible and well-tolerated with minimal additional toxicity. The complete response rate in this high-risk population compares favorably to historical results of patients receiving R-CVP. Given these results, a phase III trial comparing BR-CVP with R-CVP is planned.
In a phase 2 clinical trial, Argiris et al (2011) examined the effects of bortezomib followed by the addition of doxorubicin at progression in patients with recurrent or metastatic adenoid cystic carcinoma (ACC) of the head and neck. Eligibility criteria included incurable ACC, any number of prior therapies but without an anthracycline, unidimensionally measurable disease, Eastern Cooperative Oncology Group performance status 0 to 2, and ejection fraction within normal limits. Patients with stable disease for greater than or equal to 9 months were excluded. Patients received bortezomib 1.3 mg/m² by intravenous (IV) push on days 1, 4, 8, and 11, every 21 days until progression. Doxorubicin 20 mg/m² IV on days 1 and 8 was added at the time of progression. A total of 25 patients were enrolled, of whom 24 were eligible; the most common distant metastatic sites were the lung (n = 22) and the liver (n = 7). There was no objective response with single-agent bortezomib; best response was stable disease in 15 (71 %) of 21 evaluable patients. The median progression-free survival and OS were 6.4 months and 21 months, respectively. Of 10 evaluable patients who received bortezomib plus doxorubicin, 1 had a PR, and 6 had stable disease. The most frequent toxicity with bortezomib was grade 3 sensory neuropathy (16 %). With bortezomib plus doxorubicin, serious toxicities seen more than once were grade 3 to 4 neutropenia (n = 3) and grade 3 anorexia (n = 2). The authors concluded that bortezomib was well-tolerated and resulted in disease stabilization in a high percentage of patients but no objective responses. They stated that the combination of bortezomib and doxorubicin was also well-tolerated and may warrant further investigation in ACC.

Escobar and colleagues (2011) noted that lung cancer therapy with current available chemotherapeutic agents is mainly palliative. For these and other reasons there is now a great interest to find targeted therapies that can be effective not only palliating lung cancer or decreasing treatment-related toxicity, but also giving hope to cure these patients. It is already well-known that the ubiquitin-proteasome system like other cellular pathways is critical for the proliferation and survival of cancer cells; thus, proteosome inhibition has become a very attractive anti-cancer therapy. There are several phase I and phase II clinical trials now in non-small cell lung cancer as well as small cell lung cancer using this potential target. Most of the trials use bortezomib in combination with chemotherapeutic agents.

Dasanu (2011) stated that in the past 10 years, bortezomib moved in a step-wise fashion from a benchside promise into a bedside reality and is currently an important tool in the treatment of plasma cell disorders. This investigator focused on the relationship between bortezomib and hemolytic anemia. In animal models with lupus-like disease, this agent was shown to deplete the auto-reactive plasma cells and serum autoantibody levels. In humans, 2 isolated reports advocate the efficacy of bortezomib in autoimmune hemolytic anemia, but important concerns remain with data interpretation and length bias. Conversely, bortezomib may be causative of hemolytic anemia, as reported in a cohort of patients with chronic lymphocytic leukemia. Concerted efforts of both basic and clinical researchers are necessary to further explore the safety and effectiveness of bortezomib in non-malignant disorders, including autoimmune disorders and anemias.

An UpToDate review on “Histiocytic sarcoma” (Jacobsen, 2013) states that there are no standard treatments for histiocytic sarcoma and that patients should be encouraged to enroll in clinical trials.

The American Association for the Study of Liver Diseases and the American Society of Transplantation’s practice guideline on “Long term management of the successful adult liver transplant” (Lucey et al, 2012) made no reference to the use of bortezomib. Furthermore, an UpToDate review on ‘Treatment of acute cellular rejection in liver transplantation’ (Cotler, 2013) does not mention the use of bortezomib as a management tool.

Marginal zone lymphoma is a type of B-cell lymphoma presenting primarily in the marginal zone. There are 3 types: (i) splenic marginal zone lymphoma; (ii) extra-nodal marginal zone B cell lymphoma (MALT lymphoma or "mucosa-associated lymphoid tissue"); and (iii) nodal marginal zone B cell lymphoma (NMZL). All 3 types of marginal zone lymphoma are CD5- and CD10-negative.

Koprivnikar and Cheson (2012) noted that bortezomib is a novel proteasome inhibitor initially approved for use in MM and currently under continued investigation as a treatment for numerous subtypes of NHL. One postulated mechanism of action in NHL is the ability of bortezomib to ameliorate molecular dysregulation in NF-κB activation and regain cell cycle control. Results of
clinical trials have varied widely based on lymphoma subtype. While response to bortezomib has been dismal in patients with chronic lymphocytic leukemia and small lymphocytic lymphoma, reasonable responses have been attained in patients with mantle cell lymphoma; leading to its FDA approval as a second-line agent for the treatment of mantle cell lymphoma in 2006. Bortezomib in combination with R-CHOP has also been suggested to improve response in certain molecular subgroups of diffuse large B-cell lymphoma. The role of bortezomib in follicular and marginal zone lymphomas remains less clear.

Also, an UpToDate review on “Treatment of marginal zone (MALT) lymphoma” (Freedman and Friedberg, 2013) does not mention the use of bortezomib as a therapeutic option. Furthermore, the 2013 NCCN Drugs and Biologics Compendium does not list marginal zone lymphoma as a recommended indication of bortezomib.

An UpToDate review on “Treatment and prevention of post-transplant lymphoproliferative disorders” (Negrin et al, 2013) does not mention the use of bortezomib as a therapeutic option. Furthermore, the 2013 NCCN Drugs and Biologics Compendium does not list PTLD as a recommended indication of bortezomib.

The NCCN Drug and Biologics Compendium (2013) no longer recommends bortezomib for the following indications: splenic marginal zone lymphoma, gastric MALT lymphoma, non-gastric MALT lymphoma, and follicular lymphoma.

Claes et al (2014) noted that standard treatments for antibody-mediated rejection (AMR) -- rituximab, intravenous immunoglobulin, and/or plasmapheresis -- aim to suppress the production and modulate the effect of donor-specific antibodies (DSA) and remove them, respectively. Proteasome inhibitors (PIs) such as bortezomib are potent therapeutic agents that target plasma cells more effectively than rituximab to reduce measurable DSA production. Little is known in adults, and no data exist in children about effects of PIs to treat AMR on protective antibody titers. These researchers presented a pediatric renal transplant recipient who received bortezomib for relatively early AMR and whose antibody titers to measles and tetanus were tracked. The AMR was treated successfully, and these investigators noted no clinical decrease in the overall level of protective immunity from pre-transplant baseline levels at almost 1 year after AMR treatment cessation. The authors concluded that larger studies will elucidate more clearly how proteasome inhibition to treat AMR affects protective immunity in pediatric transplant recipients.

Eskandary et al (2014) noted that the formation of DSA and ongoing AMR processes may critically contribute to late graft loss. However, appropriate treatment for late AMR has not yet been defined. There is accumulating evidence that the bortezomib may substantially affect the function and integrity of alloantibody-secreting plasma cells. The impact of this agent on the course of late AMR has not so far been systematically investigated. The BORTEJECT Study is a randomized controlled trial designed to clarify the impact of intravenous bortezomib on the course of late AMR. In this single-center study (nephrological outpatient service, Medical University Vienna) these researchers plan an initial cross-sectional DSA screening of 1,000 kidney transplant recipients (functioning graft at greater than or equal to 180 days; estimated glomerular filtration rate (eGFR) greater than 20 ml/minute/1.73 m2). DSA-positive recipients will be subjected to kidney allograft biopsy to detect morphological features consistent with AMR. Forty-four patients with biopsy-proven AMR will then be included in a double-blind placebo-controlled intervention trial (1:1 randomization stratified for eGFR and the presence of T-cell-mediated rejection). Patients in the active group will receive 2 cycles of bortezomib (4 x 1.3 mg/m2 over 2 weeks; 3-month interval between cycles). The primary end-point will be the course of eGFR over 24 months (intention-to-treat analysis). The sample size was calculated according to the assumption of a 5 ml/minute/1.73 m2 difference in eGFR slope (per year) between the 2 groups (alpha: 0.05; power: 0.8). Secondary end-points will be DSA levels, protein excretion, measured GFR, transplant and patient survival, and the development of acute and chronic morphological lesions in 24-month protocol biopsies. The authors stated that the impact of anti-humoral treatment on the course of late AMR has not yet been systematically investigated. Based on the hypothesis that proteasome inhibition improves the outcome of DSA-positive late AMR, these investigators suggest that their trial has the potential to provide solid evidence towards the treatment of this type of rejection.
Ejaz et al (2014) stated that development of DSA after kidney transplantation is associated with reduced allograft survival. A few strategies have been tested in controlled clinical trials for the treatment of AMR, and no therapies are approved by regulatory authorities. Thus development of anti-humoral therapies that provide prompt elimination of DSA and improve allograft survival is an important goal. Proteasome inhibitor-based regimens provide a promising new approach for treating AMR. To-date, experiences have been limited to off-label bortezomib use in AMR. Key findings with PI-based therapy are that they provide effective primary and rescue therapy for AMR by prompt reduction in immuno-dominant DSA and improvements in histologic and renal function. Early and late AMR differ immunologically and in response to PI therapy. Bortezomib-related toxicities in renal transplant recipients are similar to those observed in the multiple myeloma population. Although preliminary evidence with PI therapy for AMR is encouraging, the evidence is limited. The authors stated that larger, prospective, randomized controlled trials with long-term follow up are needed. Advancement in end-points of clinical trial designs and rigorous clinical trials with more standardized adjunct therapies are also required to explore the risks and benefits of AMR treatment modalities.

Kim et al (2014) noted that AMR, also known as B-cell-mediated or humoral rejection, is a significant complication after kidney transplantation that carries a poor prognosis. Although fewer than 10% of kidney transplant patients experience AMR, as many as 30% of these patients experience graft loss as a consequence. Although AMR is mediated by antibodies against an allograft and results in histologic changes in allograft vasculature that differ from cellular rejection, it has not been recognized as a separate disease process until recently. With an improved understanding about the importance of the development of antibodies against allografts as well as complement activation, significant advances have occurred in the treatment of AMR. The standard of care for AMR includes plasmapheresis and intravenous immunoglobulin that remove and neutralize antibodies, respectively. Agents targeting B cells (rituximab and alemtuzumab), plasma cells (bortezomib), and the complement system (eculizumab) have also been used successfully to treat AMR in kidney transplant recipients. However, the high cost of these medications, their use for unlabeled indications, and a lack of prospective studies evaluating their efficacy and safety limit the routine use of these agents in the treatment of AMR in kidney transplant recipients.

An UpToDate review on "C4d staining in renal allografts and treatment of antibody mediated rejection" (Klein and Brennan, 2014) states that "An initial report also found that bortezomib, a proteosomal inhibitor, which is approved for use in multiple myeloma, may be effective in the treatment of AMR or mixed AMR and cellular rejection. Additional analysis of this agent is required to better understand its potential role".

An UpToDate review on "Acute renal allograft rejection: Treatment" (Chon and Brennan, 2014) states that "Bortezomib -- US Food and Drug Administration (FDA)-approved for treating multiple myeloma, bortezomib is a proteosomal inhibitor that causes apoptosis of mature plasma cells. Several case reports/series have demonstrated its effectiveness in treating ABMR, successfully reversing acute rejection, and/or reducing DSAs. A prospective, randomized, controlled study is needed to evaluate the efficacy and safety of this drug. At present, the optimal treatment for this entity in the setting of either acute or chronic allograft dysfunction is unknown".

Khan and colleagues (2010) noted that hyper IgG4 disease is a recently described inflammatory disease characterized by lymphoplasmacytic infiltration leading to fibrosis and tissue destruction. Whereas most cases have been successfully treated with corticosteroids, recurrent or refractory cases may benefit from alternative therapies. Bortezomib has proven to be successful in the treatment of multiple myeloma, and its mechanism indicates that it may have merit in autoimmune or other plasmacytic disorders. The authors reported a patient with recurrent pulmonary infiltration with IgG4 plasma cells, consistent with hyper IgG4 disease, who was successfully treated using a bortezomib-based combination with minimal therapy-related toxicities.

An UpToDate review on "Overview of IgG4-related disease" (Moutsopoulos et al, 2014) does not mention the use of bortezomib as a therapeutic option.

Khandelwal et al (2014) stated that therapy of refractory autoimmunity remains challenging. In this study, these investigators evaluated the therapeutic effect of bortezomib in 7 patients (median age of 9.9 years) with refractory autoimmunity. Four doses of bortezomib were administered at a dose of 1
Bortezomib (Velcade)

3 mg/m² intravenously (n = 6) or subcutaneously (n = 1) every 72 hours. Bortezomib was administered at a median of 120 days from laboratory confirmation of autoantibodies. All patients had failed 2 or more standard therapies. Rituximab was administered on the first day if B cells were present, and all patients received plasmapheresis 2 hours prior to bortezomib administration. Six patients experienced resolution of cytopenia; 2 of 6 patients experienced recurrence of cytopenia after initial response. Adverse effects include nausea (n = 1), thrombocytopenia (n = 2), Clostridium difficile colitis (n = 1), febrile neutropenia (n = 1) and cellulitis at the subcutaneous injection site (n = 1). The authors concluded that these findings suggested that bortezomib may be beneficial in the treatment of refractory autoimmunity in children. These preliminary findings need to be validated by well-designed studies.

Gomez and colleagues (2014) noted that bortezomib is currently used to eliminate malignant plasma cells in MM patients. It is also effective in depleting both allo-reactive plasma cells in adult Ab-mediated transplant rejection and their auto-reactive counterparts in animal models of lupus and myasthenia gravis (MG). In this study, these researchers demonstrated that bortezomib at 10 nM or higher concentrations killed long-lived plasma cells in cultured thymus cells from 9 early-onset MG patients and consistently halted their spontaneous production not only of autoantibodies against the acetylcholine receptor but also of total IgG. Surprisingly, lenalidomide and dexamethasone had little effect on plasma cells. After bortezomib treatment, they showed ultra-structural changes characteristic of endoplasmic reticulum stress after 8 hours and were no longer detectable at 24 hours. The authors concluded that bortezomib appears promising for treating MG and possibly other Ab-mediated autoimmune or allergic disorders, especially when given in short courses at modest doses before the standard immunosuppressive drugs have taken effect. These in-vitro findings need to be studied in future clinical trials.

In a phase II, open-label, multi-center clinical trial, Ciombor et al (2014) evaluated the effectiveness and tolerability of bortezomib in combination with doxorubicin in patients with advanced hepatocellular carcinoma, and correlated pharmacodynamic markers of proteasome inhibition with response and survival. These researchers examined the effectiveness of bortezomib (1.3 mg/m² IV on day 1, 4, 8, 11) and doxorubicin (15 mg/m² IV on day 1, 8) in 21-day cycles. The primary end-point was objective response rate. Best responses in 38 treated patients were 1 partial response (2.6 %), 10 (26.3 %) stable disease, and 17 (44.7 %) progressive disease; 10 patients were unevaluable. Median PFS was 2.2 months. Median OS was 6.1 months. The most common grade 3 to 4 toxicities were hypertension, glucose intolerance, ascites, ALT elevation, hyperglycemia and thrombosis/embolism. Worse PFS was seen in patients with elevated IL-6, IL-8, MIP-1α and EMSA for NF-κB at the start of treatment. Worse OS was seen in patients with elevated IL-8 and VEGF at the start of treatment. Patients had improved OS if a change in the natural log of serum MIP-1α/CCL3 was seen after treatment. RANTES/CCL5 levels decreased significantly with treatment. The authors concluded that the combination of doxorubicin and bortezomib was well-tolerated in patients with hepatocellular carcinoma, but the primary end-point was not met.

National Comprehensive Cancer Network guidelines (2015) recommend the use of bortezomib as subsequent therapy with or without rituximab for multicentric Castleman's disease (CD) that has progressed following treatment of relapsed/refractory or progressive disease.

CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

96372, 96374  Therapeutic drug administration
96375, 96376
96379
96401  Chemotherapy administration, subcutaneous or intramuscular; non-hormonal anti-neoplastic
Intravenous chemotherapy administration

96409, 96411
96413, 96415
96416, 96417

**HCPCS codes covered if selection criteria are met:**

J9041 Injection, bortezomib, 0.1 mg

**ICD-9 codes covered if selection criteria are met:**

200.30 - 200.36, Marginal zone lymphoma [primary cutaneous]
200.38
200.40 - 200.48 Mantle cell lymphoma
200.60 - 200.68 Anaplastic large cell lymphoma
200.80 - 200.88 Other named variants, unspecified site, extranodal and solid organ sites [primary cutaneous anaplastic large cell lymphoma (ALCL) with multifocal lesions and cutaneous ALCL with regional nodes (excludes systemic ALCL)]
202.00 - 202.08 Nodular lymphoma [cleaved follicle center cell] [second line therapy follicle center lymphoma]
202.10 - 202.18 Mycosis fungoides
202.20 - 202.28 Sezary's disease
202.80 - 202.88 Other malignant lymphomas [follicle center cell]
203.00 - 203.02 Multiple myeloma
204.80 - 204.82 Other lymphoid leukemia [adult T-cell leukemia/lymphoma]
238.6 Neoplasm of uncertain behavior of plasma cells [progressive solitary plasmacytoma]
273.3 Macroglobulinemia [Waldenstrom's]
277.30 - 277.39 Amyloidosis [systemic light chain]

**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**

042 Human immunodeficiency virus (HIV) disease
079.53 Human immunodeficiency virus, type 2 (HIV-2)
140.0 - 200.28, Neoplasms
200.37, 200.50 -
200.58, 200.70 -
201.98, 202.30 -
202.68, 202.90 -
202.98, 203.10 -
204.22, 204.90 -
238.5, 238.71 -
239.9
279.00 - 279.9 Disorders involving the immune mechanism
283.0 Autoimmune hemolytic anemias
340 Multiple sclerosis
358.00 - 358.01  Myasthenia gravis
493.00 - 493.92  Asthma
711.00 - 716.99  Arthropathies
785.6  Enlargement of lymph nodes [Castleman's disease]
996.80 - 996.89  Complications of transplanted organ

Other ICD-9 codes related to the CPB:
V58.11 - V58.12  Encounter for antineoplastic chemotherapy and immunotherapy

The above policy is based on the following references:


75. National Horizon Scanning Centre. Bortezomib (Velcade) for multiple myeloma within a transplant setting. Horizon Scanning Review. Birmingham, UK: National Horizon Scanning Centre (NHSC); April 2011.


89. Negrin RS, Brennan DC, Jessup M. Treatment and prevention of post-transplant lymphoproliferative disorders. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed May 2013.

90. Cotler SJ. Treatment of acute cellular rejection in liver transplantation. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed May 2013.


96. Klein CL, Brennan DC. C4d staining in renal allografts and treatment of antibody mediated rejection. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed May 2014.


98. Moutsopoulos HM, Fragoulis GE, Stone JH. Overview of IgG4-related disease. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed May 2014.


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