Thrombotic Microangiopathy with Targeted Cancer Agents

John A. Blake-Haskins1,2, Robert J. Lechleider2, and Robert J. Kreitman3

Abstract

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are clinically similar disorders characterized by microvascular thrombosis, hemolysis, thrombocytopenia, and end-organ damage. Although they may present with overlapping symptoms, multiple etiologies have been proposed for these thrombotic microangiopathies (TMA). Chemotherapy-induced TMA, which has been described with the use of mitomycin, gemcitabine, and other drugs, has a poor prognosis. Recently, reports of TMA associated with targeted cancer agents have surfaced in the literature. We discuss the clinical presentation, outcome, and etiology of TMA reported with the use of immunotoxins, monoclonal antibodies, and tyrosine kinase inhibitors. A search of PubMed and meeting abstracts was conducted for cases of TMA with the use of targeted cancer agents. The defining symptoms, laboratory values, time to onset, and patient outcomes were compiled. Consistent definitions of TMA and grading of severity in these cases are lacking. However, presentation of TMA in these cases revealed the importance of monitoring for renal toxicity, hemolysis, and thrombocytopenia. Patient outcomes seem to differ from those seen in cases of chemotherapy-induced TMA and may reflect a different underlying etiology. Little is known about the pathogenesis of TMA with targeted cancer agents. In contrast to chemotherapy-induced TMA, partial to full reversibility may be a common outcome. However, further research is warranted into optimal management of patients diagnosed with TMA following treatment with targeted agents. Clin Cancer Res; 17(18); 5858–66. ©2011 AACR.
Translational Relevance

Thrombotic microangiopathies (TMA) are known to occur in malignancy and have been linked to cytotoxic chemotherapy, including mitomycin and gemcitabine. The pathogenesis of chemotherapy-induced TMA is likely due to direct endothelial cell injury. Recently, case reports of TMA related to the use of targeted cancer agents have also surfaced in the literature. Little is known about the etiology of TMA in these cases. Herein, we review the clinical presentation, outcome, and proposed mechanisms of TMA associated with the use of monoclonal antibodies, immunotoxins, and tyrosine kinase inhibitors.

displaying globotriaosylceramide receptors (Gb3 and Gb4), including the glomerular endothelial and epithelial cells (1, 8). The toxins result in cell death because of inhibition of protein formation and result in the release of TNF-α, interleukin (IL)-1, IL-6, and IL-8. These inflammatory cytokines may potentiate renal injury secondary to infiltration by neutrophils and lead to upregulation of the Gb3 receptor. In addition, TNF-α and IL-8 have been shown to cause vWF secretion, whereas IL-6 inhibits cleavage of ultralarge multimers in vitro (9). Other direct effects of Stx1 include stimulation of endothelial cells to express tissue factor and secrete vWF, as well as activation of platelets (1, 10).

The etiology of the remaining 10% of ‘atypical’ HUS (aHUS) cases is heterogeneous and largely linked to mutations in factors of the complement system (11, 12). The end result of these mutations is an overactive complement system causing endothelial cell damage, detachment, and eventual activation of the coagulation cascade. The alternative pathway of complement may play a role in typical HUS as well. Orth and colleagues showed in vitro activation of complement by Stx2 and proposed that complement may contribute to kidney damage in typical HUS (8).

Finally, both TTP and HUS have been associated with malignancy, hematopoietic stem cell transplantation, and specific medications. Historically, review articles of drug-induced TMA have focused on immunosuppressants, anti-aggregating agents, and cytotoxic chemotherapy (13–16). Among cytotoxic chemotherapy agents, mitomycin and gemcitabine (Table 1) are particularly associated with TMA, and the U.S. Food and Drug Administration (FDA)–approved labeling warns of this risk (17, 18).

The etiology of chemotherapy-induced TMA is thought to be nonspecific, toxic insult to the microvasculature. Direct endothelial cell injury has been reproduced in an animal model of mitomycin-induced HUS and most likely plays a central role (14). Following endothelial injury and exposure of the subendothelium, platelet activation and subsequent clotting within the microvasculature may occur.

Thrombotic Microangiopathy Induced by Targeted Agents

Immunotoxins

Immunotoxins are proteins comprised of a cell-selective ligand chemically conjugated or genetically fused to a toxin (19, 20). The cell-selective portion of the immunotoxin is commonly a monoclonal antibody, antibody fragment, growth factor, or cytokine that binds to specific cell-surface receptors. Once bound to a surface antigen, immunotoxins enter the target cell through endocytosis and undergo processing to release the toxin into the cytosol (21). Several of these agents have shown promising activity in clinical trials; however, TMA has been reported with their use, and the mechanism behind this adverse effect is not completely understood.

CAT-3888, formerly called BL22, is an immunotoxin that targets CD22 and has been investigated for the treatment of hairy cell leukemia (HCL), non-Hodgkin lymphoma, and chronic lymphocytic leukemia (22–24). During phase I and II testing of CAT-3888, 9 cases of grade 1 to 4 HUS were reported in 8 of the 82 subjects treated (22–24). In addition, HUS was reported in 1 of 2 HCL patients treated by special exemption prior to the opening of the phase II trial (22). Subjects in the phase I study were treated with 6 to 12 days of plasmapheresis, whereas those on the phase II study were given only supportive care. HUS was completely reversible in 9 of the 10 cases, regardless of treatment, with up to 57 months of follow-up in the phase I study. Note that the first of the 10 cases was not evaluable for reversibility because the patient had an aggressive lymphoma and refused additional treatment for rapidly progressive disease. However, this patient, who became anuric with HUS, resumed normal urination prior to dying of progressive lymphoma. ADAMTS13 was reported to be adequate in all cases, suggesting that ultralarge multimers of vWF were not circulating in these patients.

Moxetumomab pasudotox, formerly known as CAT-8015 or HA22, is an affinity-matured recombinant anti-CD22 immunotoxin that offers enhanced binding affinity compared with CAT-3888 (25). A preliminary report of an ongoing phase I trial in HCL suggests that HUS may occur with lower frequency in patients treated with moxetumomab pasudotox compared with CAT-3888 (26). Two of 28 subjects treated had experienced reversible, grade 2 HUS following moxetumomab pasudotox administration. The clinical presentation of HUS seems to be similar to that seen in subjects treated with CAT-3888. However, in both of these cases, the peak creatinine was <2.0 mg/dL and the nadir platelet count was >100,000/μL.

Combotox is an investigational combination of 2 deglycosylated ricin A chain (dγA) immunotoxins directed against CD19 and CD22 (27). This combination has been evaluated in a phase I study (N = 22) in which 2 cases of HUS were observed (27). Both subjects were reported to have followed a similar clinical course of vascular leak, respiratory insufficiency, HUS, and eventual death. The severe morbidity and mortality in these subjects may have
been related to complicating vascular leak syndrome (VLS) rather than HUS. In fact, VLS has proved to be a prominent toxicity for large, conjugated immunotoxins because of either their long plasma half-lives or residues that bind to endothelial cells (28). The authors of this study suggest that HUS in these patients may be associated with low or absent levels of circulating tumor cells and possibly with high serum concentrations of the immunotoxins.

DAB486IL-2 is a recombinant immunotoxin targeting IL-2 with the membrane translocation and ADP-ribosylation domains of diphtheria toxin, and it is the precursor of DAB389IL-2 (denileukin diftitox; ref. 29). During a phase I trial (N = 23) of DAB486IL-2, the maximum tolerated dose was determined by HUS toxicity in 2 patients (30). Similar toxicity was noted in 1 patient in a later phase II study (N = 14; ref. 31). The HUS experienced by this patient was

Figure 1. Proposed pathophysiology of TMAs. A, formation of pathogenic thrombi in TMA may arise from reduced ADAMTS13 activity. ADAMTS13 bound to the surface of endothelial cells can cleave ultralarge multimers of vWF. When the activity of ADAMTS13 is reduced because of anti-ADAMTS13 antibodies or an inherited deficiency, the uncleaved multimers of vWF induce platelet aggregation. B, in atypical HUS, mutations in complement proteins lead to unregulated formation of C5a and C5b-9 (membrane-attack complex). Recruitment of neutrophils, endothelial cell injury, and exposure of the subendothelium results in a prothrombotic state. C, drug cytotoxicity can also result in direct injury to the endothelium and lead to TMA. The exact pathogenesis of TMA in these cases is unknown but may involve decreased levels of prostacyclin, secretion of vWF, or exposure of the subendothelium leading to thrombus formation.
Apolizumab (Hu1D10) is a humanized monoclonal antibody against an antigen on the β chain of HLA-DR called 1D10. HUS was observed to be a dose-limiting toxicity in 1 subject during a phase I and II trial (N = 23) of apolizumab (34). No schistocytes were observed by peripheral blood smear.

HUS has also been reported in a phase I study of apolizumab plus rituximab (35). In this study, subjects were administered weekly doses of 375 mg/m² rituximab followed by increasing doses of apolizumab. The dose-limiting toxicity was reported to be HUS, but the number of subjects experiencing HUS and their clinical presentation were not described. The authors reported that 1D10 was found on endothelial cells and might have played a role in the pathogenesis of HUS in these patients.

Alemtuzumab is a monoclonal antibody that targets CD52 on the surface of B and T lymphocytes. During an experimental study (N = 41) in rheumatoid arthritis, a 49-year-old female developed HUS after receiving her second dose of alemtuzumab (36). Following 2 days of plasmapheresis, renal function returned to normal and the patient made a complete recovery. Alemtuzumab has been noted to cause elevation of serum TNF-α and IL-6. Similar to one of the proposed mechanisms behind TMA following treatment with cytotoxic chemotherapy, cytokine release may be partly responsible for HUS in this subject.

### Table 1. Characteristics of TMA associated with mitomycin and gemcitabine

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Incidence</th>
<th>Clinical presentation</th>
<th>Onset</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitomycin</td>
<td>2–15%</td>
<td>Severe MAHA: thrombocytopenia; renal dysfunction; elevated lactate dehydrogenase; elevated bilirubin; pulmonary edema</td>
<td>Cumulative doses &gt;30 mg/m² and &gt;1 year of treatment</td>
<td>Mortality ~75% related to renal failure</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>0.25–0.4%</td>
<td></td>
<td>2,000–48,000 mg/m² and 5–8 months of treatment</td>
<td>Mortality ~60%; renal failure 34–69%; reversal of anemia and thrombocytopenia may be common</td>
</tr>
</tbody>
</table>

NOTE: Data summarized in this table are from references 13–16.

described as “mild”; it was reversible and did not recur upon retreatment at a reduced dose. Recurrent HUS may have been avoided in this case because of the presence of antitoxin antibodies, but the authors do not report on levels of neutralizing antibodies in this study. To our knowledge, no published case reports associate HUS with denileukin difftox.

The mechanism behind TMA induced by immunotoxins is not well understood. Animal models of ricin-induced HUS provide evidence toward a pathway for renal injury (32, 33). Administration of unconjugated ricin to mice and rats leads to the development of a syndrome closely resembling HUS in humans. The animals develop glomerular thrombosis, renal failure, hemolysis, and thrombocytopenia. Accompanying these pathologic changes are rapid increases in the proinflammatory cytokines MCP-1, TNF-α, IL-1β, and IL-6. Upregulation of these cytokines may promote an inflammatory environment and subsequent infiltration of the glomeruli with macrophages that stimulate secretion of vWF.

Each of the above-mentioned immunotoxins uses different protein toxins and targets different cellular receptors. Messmann and colleagues speculate that both targeted and nontargeted endothelial cell binding of toxins may play an integral role in the pathogenesis of HUS with the use of Combotox (27). Identification of low levels of CD19, CD22, and IL-2 receptors on glomerular endothelial cells would support the theory of targeted cell death in immunotoxin-induced TMA. However, the presence of CD22 on glomerular endothelium seems unlikely to be a major mechanism, as one would expect moxetumomab pasudotox to cause HUS at lower concentrations than CAT-3888 because it binds with 15-fold higher affinity to this cell-surface receptor. Other mechanisms, such as cross-reactivity to a different target or nonspecific uptake into cells by pinocytosis, may possibly be related to immunotoxin-induced HUS (21).

### Immunotherapy

Apolizumab (Hu1D10) is a humanized monoclonal antibody against an antigen on the β chain of HLA-DR called 1D10. HUS was observed to be a dose-limiting effect. In an experimental study (21), a complete recovery was made a complete recovery. Alemtuzumab has been noted to cause elevation of serum TNF-α and IL-6. Similar to one of the proposed mechanisms behind TMA following treatment with cytotoxic chemotherapy, cytokine release may be partly responsible for HUS in this subject.

### Anti-VEGF therapy

Among the targeted oncology drugs associated with TMA, those that inhibit the VEGF pathway are the most widely studied. A series of 21 case reports of TMA associated with VEGF inhibition have been published in the past 5 years (37–44). These cases have been observed with the use of multiple anti-VEGF agents, suggesting a potential class-wide effect.

Eremina and colleagues describe 6 biopsy-documented cases of TMA resembling HUS following bevacizumab administration (39). All of the patients described in this series developed proteinuria or increased serum creatinine following the initiation of bevacizumab, ultimately leading to renal biopsy. However, beyond these indications of renal injury, the clinical presentation was not uniform across all patients. Following discontinuation of bevacizumab, improvement in renal function was noted, suggesting at least partial reversibility.
Reports of TMA are not limited to bevacizumab, as they also appear for agents that target the VEGF pathway by different mechanisms. Three cases of renal TMA have been reported with the use of sunitinib (37, 41, 42). One case of TMA associated with aflibercept has also been reported (44). Combination therapy of bevacizumab and sunitinib in a phase I trial resulted in TMA of greater severity. Feldman and colleagues report 5 cases of MAHA along with 3 additional cases of "MAHA-like features" in a trial of 25 patients (43). MAHA was graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 guidelines for TMA (45). Two patients with grade 3 MAHA also developed neurologic symptoms. Those patients described as having MAHA-like features presented similarly, but without schistocytosis or neurologic symptoms. Following discontinuation of anti-VEGF therapy, all subjects showed improvement. The high rate of TMA in this trial (8 of 25 subjects) and the development of extra-renal complications in 2 subjects indicate a more severe manifestation of TMA with combined blockade of the VEGF pathway.

Eremina and colleagues have provided a detailed proposal for a mechanism of VEGF-induced TMA. They propose that inhibition of VEGF in the glomerular microvasculature prevents the formation and maintenance of a healthy, fenestrated endothelium (39). Without active VEGF signaling, the endothelium is compromised, along with the filtration barrier of the glomerulus. The authors’ proposed pathway to TMA is supported by elegant animal models in which only the renal podocytes are genetically deprived of the VEGF gene. In this model, the knockout mice developed features in line with those seen in human cases of bevacizumab-induced TMA.

**Imatinib**

Imatinib inhibits multiple tyrosine kinase inhibitors, including bcr-abl, those for platelet-derived growth factor stem cell factor, and c-kit, and it has been associated with TMA. Al Aly and colleagues report on a 22-year-old woman with hypereosinophilic syndrome who developed TMA after receiving imatinib (46). ADAMTS13 activity was below the normal range, whereas the ADAMTS13 inhibitor level was markedly elevated. The patient was treated with plasma exchange and hemodialysis, leading to a hematologic recovery but persistent renal impairment.

**Discussion**

**Diagnosing thrombotic microangiopathy**

Although a diagnosis of TMA is centered on recognizing microvascular thrombosis, red blood cell destruction, and platelet consumption, no guidelines currently exist to completely define TMA or its severity. The difficulty in evaluating TMA is reflected in the similar CTCAE definitions of HUS and TTP (45, 47). Moreover, the CTCAE fails to provide more than a cursory outline of severity grading for TMA. Further delineation of critical signs and symptoms of HUS and TTP are warranted considering their heterogeneous causes and prognoses. Severity defined by laboratory value cut-offs would be particularly beneficial. An example of a more detailed scheme for grading TMA is shown in Table 2.

**Table 2. Proposed detailed grading of thrombotic microangiopathies**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1: Evidence of erythrocyte destruction, without clinical consequences</td>
<td>The appearance of schistocytosis (≥5/HPF) in a patient with no schistocytosis at baseline or an increase (≥5/HPF) in the frequency of schistocytes over baseline</td>
</tr>
<tr>
<td>Grade 2: Laboratory findings without clinical consequences</td>
<td>Microangiopathic anemia (schistocytosis; Hgb by 1 g/dL) and mild renal insufficiency (creatinine, grade 1)</td>
</tr>
<tr>
<td>Grade 3: Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)</td>
<td>Microangiopathic anemia (schistocytosis; Hgb by 1 g/dL), and either grade 4 thrombocytopenia or moderate renal insufficiency (creatinine, at least grade 2 if normal at baseline or at least one grade worse than baseline)</td>
</tr>
<tr>
<td>Grade 4: Laboratory findings with life-threatening or disabling consequences (e.g., CNS hemorrhage and/or bleeding, or thrombosis and/or embolism, or renal failure)</td>
<td>Microangiopathic anemia (schistocytosis; Hgb by 1 g/dL), and either clinically significant hemorrhage requiring intervention or renal insufficiency requiring intervention (i.e., plasmapheresis, dialysis)</td>
</tr>
<tr>
<td>Grade 5: Death</td>
<td>Death</td>
</tr>
</tbody>
</table>

**Abbreviations:** CNS, central nervous system; HPF, high-powered field; Hgb, hemoglobin; ↓, decreasing; ↑, increasing.
Table 3. Comparison of thrombotic microangiopathy associated with targeted cancer agents

<table>
<thead>
<tr>
<th>Targeted therapy</th>
<th>CAT-3888</th>
<th>Moxetumomab pasudotox</th>
<th>Combotox DAB486IL-2</th>
<th>Apolizumab</th>
<th>Alemtuzumab</th>
<th>Bevacizumab</th>
<th>Sunitinib</th>
<th>Aflibercept and sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>≥3</td>
<td>1</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Time to onset</td>
<td>2–3 cycles</td>
<td>3–5 cycles</td>
<td>3–5 days</td>
<td>NR</td>
<td>11 doses</td>
<td>2 doses</td>
<td>4–29 doses</td>
<td>2 weeks to 7 months</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Thrombocytopenia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Decreased Hgb</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>+</td>
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<tr>
<td>Hemolysis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Elevated reticulocyte count</td>
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<tr>
<td>Elevated bilirubin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
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<td>+</td>
<td>+</td>
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<tr>
<td>Decreased haptoglobin</td>
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<td></td>
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<tr>
<td>Schistocytes</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
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<tr>
<td>Elevated LDH</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Elevated creatinine</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Proteinuria</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
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<tr>
<td>Decreased urine output</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Decreased albumin</td>
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</tr>
<tr>
<td>Pulmonary</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
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<tr>
<td>Edema</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
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<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
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<td>+</td>
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<tr>
<td>Neurologic</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
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<td>+</td>
<td>+</td>
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<tr>
<td>Biopsy confirmation</td>
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</tr>
<tr>
<td>Outcome</td>
<td>9 of 10 fully reversible, 1 death due to progressive disease</td>
<td>2 of 2 fully reversible</td>
<td>2 of 2 deaths</td>
<td>1 death fully reversible (others NR)</td>
<td>Fully reversible</td>
<td>1 fully reversible, 7 partially reversible with persistent proteinuria, 1 death due to progressive disease</td>
<td>3 of 3 fully reversible</td>
<td>Partially reversible, 5 NR (hematologic recovery; dialysis dependent)</td>
</tr>
</tbody>
</table>

Abbreviations: NR, not reported; Hgb, hemoglobin.
following anti-VEGF therapy, schistocytes were only noted in 4 of 10 cases. However, doing biopsies to evaluate TMA is not appropriate for all patients. Thrombocytopenia was noted in most cases of TMA, but with varying severity. In the cases reviewed, consequences of thrombocytopenia, such as petechiae and hemorrhage, were not discussed. Strict monitoring of renal function, platelet count, and for signs of nonautoimmune hemolytic anemia is recommended for patients receiving these targeted therapies.

### Treatment and outcome

Many interventions for TMA have been described (Table 4). Optimal treatment of drug-induced TMA, and especially TMA induced by targeted agents, has yet to be proved. In the cases summarized in this review, plasma exchange and plasmapheresis were both used, but they may not be necessary if ADAMTS13 activity is unaltered in these patients. As noted for the cases of HUS associated with CAT-3888 and moxetumomab pasudotox, supportive care alone resulted in full recovery for several subjects. An advantage of these molecules compared with larger immunotoxins is their smaller size (~62 kDa), leading to relatively rapid (2–3 hours) half-life and fewer complications because of vascular leak syndrome. Until more is known about the mechanism of TMA following the use of targeted agents, immediate discontinuation of the offending drug may be the most important step in treatment. For patients with aHUS refractory to plasma exchange, eculizumab has resulted in clinical remission in selected cases (48–50). Likewise, rituximab has shown a high response rate without severe toxicity in a trial of refractory TTP (N = 24) and should be considered for these patients (51).

Reintroducing the drug at lower dose levels may be a strategy to avoid recurrent TMA, while allowing for continued treatment. Retreatment following TMA has been safely carried out with CAT-3888, DAB486IL-2, and bevacizumab (24, 31, 39). However, it may be difficult to choose an appropriate dose for reintroduction, and careful consideration of the potential risks and benefits to the patient should take place.

TMA with several of the targeted cancer agents seems to be reversible. HUS was fully reversible in 11 of the 12 subjects administered the immunotoxins CAT-3888 and moxetumomab pasudotox, at least 1 of the subjects given DAB486IL-2, and in the 1 case report involving alemtuzumab. Partial to full reversibility was also noted for anti-VEGF–treated patients; however, persistent proteinuria was common. Deaths were reported for both HUS cases seen with Combotox and in 1 of the cases of apolizumab treatment.

Unlike TMA induced by mitomycin and gemcitabine, there may not be a correlation between dose, cumulative dose, or time to onset and the use of targeted therapy. Perhaps any relationship between dose and time on therapy will become clearer as additional case reports are compiled.

### Table 4. Managing thrombotic microangiopathies

<table>
<thead>
<tr>
<th>TMA</th>
<th>Intervention</th>
<th>Proposed mechanism of action</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial TTP</td>
<td>Infusions of fresh-frozen plasma</td>
<td>Source of exogenous ADAMTS13</td>
<td>Reverses or prevents episodes of TTP in these cases</td>
</tr>
<tr>
<td>Acute, acquired TTP</td>
<td>Plasma exchange</td>
<td>Removal of ultralarge multimers of vWF, immune complexes, and autoantibodies to ADAMTS13</td>
<td>Survival improved from ~10% to 70–90%</td>
</tr>
<tr>
<td>Acute, acquired TTP</td>
<td>Glucocorticoids or splenectomy</td>
<td>Decreased formation of immune complexes</td>
<td>Has been used in combination with plasma exchange in severe cases</td>
</tr>
<tr>
<td>Acute, acquired TTP</td>
<td>Rituximab</td>
<td>Depletion of B cells responsible for production of anti-ADAMTS13 antibodies</td>
<td>Has been successfully used in TTP refractory to plasma exchange and in relapsed TTP</td>
</tr>
<tr>
<td>aHUS</td>
<td>Eculizumab</td>
<td>Binds complement protein C5, preventing formation of C5a and C5b-9 (the membrane-attack complex)</td>
<td>Has been used in aHUS refractory to plasma exchange and following renal transplant to prevent recurrent aHUS</td>
</tr>
<tr>
<td>&quot;Typical&quot; HUS</td>
<td>Dialysis</td>
<td>Renal replacement therapy</td>
<td>Dialysis may not be necessary in mild cases</td>
</tr>
</tbody>
</table>

**NOTE:** Data summarized in this table are from references 1, 15, and 48–51.
TMA with Targeted Cancer Agents

Conclusions

As strategies to treat cancer begin to incorporate more targeted therapeutics, such as monoclonal antibodies, immunotoxins, and small molecule inhibitors, it will be important to recognize the unique toxicities that accompany their use. TMA is one such toxicity that has been associated with these targeted agents, and research into its pathogenesis is in its infancy. Detailed evaluation of biopsy results, laboratory values, and ADAMTS13 levels of future cases may be warranted. In addition, animal models such as those used by Eremina and colleagues may help to further define the mechanisms of these disorders (39). Preliminary analysis seems to show a reversible course of TMA in the majority of patients described in this review.

However, until preferable methods of prevention and treatment are determined, management of TMA should focus on strict monitoring for and early recognition of the signs and symptoms of HUS or TTP.

Disclosure of Potential Conflicts of Interest

J.A. Blake-Haskins: postdoctoral fellow sponsored by MedImmune, LLC. R. Lechleider: employee, MedImmune, LLC. However, the majority of the agents reviewed have no relation to MedImmune. R.J. Kreitman is a coinventor on the government-owned patent for anti-CD22 recombinant immunotoxins, although these agents constitute a minority of those reviewed.

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