Mycosis fungoides (MF) usually has an indolent course,^1^ with a disease-specific 5-year survival rate of 88%. However, approximately 30% of all patients with MF experience disease progression or die of the disease.^2^ CD30 expression is associated with a significantly reduced disease-specific survival and is often associated with histologically detectable large cell transformation, hallmarking a more aggressive clinical course.^

Brentuximab vedotin (Adcetris) is an anti-CD30 antibody conjugated by a protease-cleavable linker to monomethylauristatin E, which inhibits the polymerization of microtubuli, has produced promising results in phase 2 trials in CD30^+^ Hodgkin lymphoma and anaplastic large cell lymphoma.

We describe 4 patients with advanced CTCL, 3 with MF and 1 with Sézary syndrome, who were treated with brentuximab. All patients had received multiple previous systemic therapies. In 2 cases of MF, a remission enabling subsequent allogeneic stem cell transplantation was achieved.

Brentuximab is a well-tolerated, promising new treatment option for advanced CTCL that can be integrated in an allogeneic stem cell transplantation plan by selectively depleting malignant CD30^+^ cutaneous lymphoma cells.

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Brentuximab vedotin (Adcetris) is an anti-CD30 antibody conjugated by a protease-cleavable linker to monomethylauristatin E, developed for the treatment of systemic large cell anaplastic and Hodgkin lymphoma, with promising phase 2 trial results.^

Therefore, brentuximab provides hope for a targeted therapy in transformed MF. So far, no reports on its clinical effectiveness in MF have been published. Although large trials evaluating the effect of brentuximab in CD30^+^ MF are currently under way, we present our experience with 4 patients with rapidly progressing advanced MF and a poor prognosis in whom all currently available and approved therapeutic options had failed. Two of these patients were treated with bridge-to-transplantation therapy with subsequent allogeneic stem cell transplantation, a use for brentuximab so far not published in a clinical setting.

We report a case series of 4 patients who were treated with brentuximab as salvage therapy in a compassionate use program (Table). Patients received 3 cycles of 1.8 mg/kg of brentuximab vedotin intravenously except patient 4, who received 4 cycles. The intervals between 2 cycles were spaced roughly 21 days apart. The mean follow-up period was 7.4 months (range, 4.7-11.8 months).

**Patient 1**

Patient 1 was a 53-year-old woman with stage IVA MF, first diagnosed in 2004 as stage IB MF (eFigure in the Supplement). Numerous previous therapies had failed, including psoralen-UV-A (PUVA), UV-B, low-dose methotrexate, vorinostat, bexarotene, forodesine, interferon alfa, multiple chemotherapies (including liposomal doxorubicin hydrochloride^6^ and cyclophosphamide, hydroxydaunorubicin, vincristine [Oncovin], and prednisone [CHOP]), and multiple rounds of radiotherapy. The disease progression to stage IVA MF was documented on March 24, 2012, when malignant MF tumor cells were detected in an axillary lymph node. At the same time, ma-
lignant T cells in the lymph node biopsy stained positive for CD30, and the diagnosis of transformed MF was established. At that point, skin biopsy results were still negative for CD30. Nevertheless, because of failure of all other available treatments and progressive disease, as well as a lymph node that tested positive for CD30+ malignant MF cells of the same clone (same T-cell receptor γ-specific polymerase chain reaction clone Vγ9), systemic treatment with brentuximab was initiated. Unfortunately, after 3 cycles of 1.8 mg/kg of brentuximab vedotin, treatment was stopped because of progression of the malignant generalized lymphadenopathy in addition to persistent pruritus and erythroderma. In a later skin biopsy specimen, more than 75% of infiltrating neoplastic cells stained positive, which allowed for a subsequent therapy with doxorubicin, paclitaxel, and cyclophosphamide 1 month later. Subsequently, an allogeneic stem cell transplantation with reduced-intensity conditioning (fludarabine, busulfan, and antithymocyte globulin) from an HLA-and ABO-identical sibbling could successfully be performed. The follow-up period for brentuximab was 11.8 months, and no related adverse events were reported.

**Patient 2**

Patient 2 was a 40-year-old man with CD30+ stage IVb MF granulomatous slack skin. He was originally diagnosed as having stage Ib MF in 1994. CD30+ large cell transformation was first documented on July 27, 2012, in a lymph node biopsy specimen. Previous treatments with topical corticosteroids, PUVA, interferon alfa, and chemotherapies, including gemcitabine and liposomal doxorubicin, produced remission, but ultimately there was disease progression. Systemic involvement of the spleen and subsequently the liver was recorded December 6, 2012. The patient was scheduled for allogeneic stem cell transplantation, and brentuximab vedotin therapy was initiated at a standard dose of 1.8 mg/kg as salvage therapy. After 3 cycles, a mixed response with a sufficient tumor burden reduction was observed, which allowed for a subsequent therapy with doxorubicin, paclitaxel, and cyclophosphamide 1 month later. Subsequently, an allogeneic stem cell transplantation with reduced-intensity conditioning (fludarabine, busulfan, and antithymocyte globulin) from an HLA- and ABO-identical sibling could successfully be performed. Cutaneous CD30+ relapse of MF occurred in the first weeks after stem cell transplantation. The skin was efficiently cleared from MF plaques by reducing immunosuppression with consecutive isolated acute graft-vs-host disease (GVHD) of the skin. However, systemic visceral involvement progressed. Although the patient had severe corticosteroid-refractory GVHD, additional treat-
Patient 3
Patient 3 was a 73-year-old man first diagnosed as having leukemic cutaneous T-cell lymphoma (CTCL) on December 17, 2010. Stage IVa Sézary syndrome was diagnosed on January 26, 2011. The hematologic involvement of his disease was treated with photopheresis, bexarotene, and alemtuzumab, which led to a substantial reduction of the malignant T-cell burden in his blood. However, the cutaneous symptoms failed to respond. Interestingly, the malignant infiltrate in his skin had a preponderance of CD30+ cells (75% of T cells), which encouraged us to switch from alemtuzumab mainly used for his blood disease to brentuximab for his skin disease. He received his first dose of 1.8 mg/kg of brentuximab vedotin 2.4 years after the initial diagnosis of leukemic CTCL had been made. Despite rapid response of his skin affliction within the second week and unchanged normal blood values, disease recurrence of the skin occurred soon after, and brentuximab therapy had to be stopped after the second cycle because of worsening of the skin disease with appearance of erosive erythroderma. After a follow-up period of 4.7 months, the patient died even after additional treatment with liposomal doxorubicin.

Patient 4
Patient 4 was a 36-year-old man with CD30+ stage IVa MF granulomatous slack skin. He was first diagnosed as having stage Ib MF in 1996. CD30+ transformation with involvement of the lymph nodes (stage IVa) was detected on September 20, 2012. Treatment history for MF included interferon alfa, imiquimod, radiotherapy, and chemotherapy (dexamethasone, cytarabine, and cisplatin and CHOP). A total of 17.1 years had elapsed until the first cycle of brentuximab. He received in total 4 cycles of 1.8 mg/kg. The patient had a complete remission and subsequently underwent an allogeneic stem cell transplantation with reduced-intensity conditioning (fludarabine, busulfan, and antithymocyte globulin) from an unrelated, HLA-identical (10/10 matched), ABO-minor incompatible donor. Early lymphoma relapse on the skin after day 10 cleared on reduction of the immunosuppression, inducing acute GVHD of the skin. The patient was in continued complete remission at the 8-month follow-up period (Figure 1 and Figure 2). No brentuximab-related adverse events were recorded.

Discussion
Life expectancy decreases markedly in late-stage MF as soon as lymph nodes or visceral organs are involved.7 Furthermore, large cell transformation and the appearance of CD30+ malignant T cells are well-established markers of bad prognosis. Treatment options for advanced stages of MF are limited and have relatively low long-term remission rates without improved overall survival rates.8 Targeting CD30+ neoplastic cells with brentuximab has already proved to be highly promising in both Hodgkin lymphoma and systemic anaplastic large cell
lymphoma, which raised expectations for its use in CD30+ transformed CTCL. Brentuximab is currently under clinical investigation in larger phase 2 and phase 3 studies for CD30+ CTCL, and interim results look promising. Recently, successful treatment of a patient with Sézary syndrome with brentuximab has been reported.

We summarize the clinical outcome in the 4 patients treated with brentuximab in a compassionate use setting. However, compared with previously published response rates for Hodgkin lymphoma and anaplastic large cell lymphoma of 75% and 86%, respectively, with mean durations of response for all patients of 20.5 months and 13.2 months and disease control in 99% and 97% of patients, in our small case series, response rates were more moderate: 2 of 4 patients responded considerably; as a result, both subsequently underwent allogeneic hematopoietic stem cell transplantations. One patient achieved complete remission with no detectable disease at the end of the follow-up period. The other patient had a progression of CD30+ MF after stem cell transplantation, refused subsequent administration of brentuximab, and died. The 2 patients who did not respond or who had only a very limited response remained recalcitrant to all available treatment options and have since died.

In contrast to preliminary data from other trials, our results did not hint at a possible correlation between the overall response rate to brentuximab and the level of CD30 expression. In contrast to current primary indications for brentuximab, Hodgkin lymphoma, and systemic anaplastic large cell lymphoma, CD30 positivity and large cell transformation are only partly observed in MF. Furthermore, even in the case of CD30+ MF, usually only part of the malignant cells express this marker, which may account for the difference in clinical...
efficacy. Furthermore, all 4 patients in our series were in advanced disease stages and had undergone multiple treatments before being treated with brentuximab.

We found that in 2 heavily pretreated patients with advanced MF, brentuximab was successfully used as an effective neoadjuvant treatment, reducing the disease burden and enabling allogeneic stem cell transplantation. A further therapeutic possibility could be the use of brentuximab after allogeneic stem cell transplantation to treat CD30+ persistent disease or relapse. Concerns that treatment of posttransplantation, relapsed CD30+ systemic hematologic malignant tumors with brentuximab could result in the induction or worsening of GVHD could not be confirmed in a series of 25 patients with Hodgkin lymphoma.14 Furthermore, a recent case series backed by experimental investigations found that brentuximab led to an induction of tumor-specific immunity and sustained clinical remission of patients with relapsed Hodgkin lymphoma treated with brentuximab and donor lymphocyte infusions in a post-allogeneic stem cell transplantation setting.14 Therefore, one can speculate that brentuximab may also be effective by strengthening the graft-vs-leukemia effect.

Conclusions

Taken together, our series of patients suggest a therapeutic role for brentuximab in CD30+ MF. Most important, brentuximab may turn out to be the treatment of choice for advanced stages of CD30+ MF, opening a window of opportunity by reducing or depleting malignant cells and thus enabling curative hematopoietic stem cell transplantation with an improved toxicity profile compared with standard chemotherapies.

REFERENCES