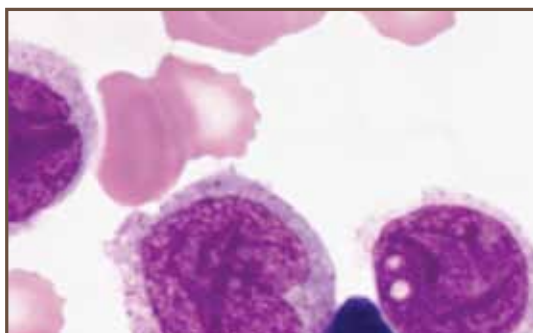


Specialists in Hematologic Malignancies and Stem Cell Transplantation

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## Novel Therapy for Hodgkin Lymphoma Patients



### JEFFREY MATOUS, MD

The year 2011 witnessed the FDA approval of a novel therapy for patients for whom we have desperately needed new options: those Hodgkin Lymphoma (HL) patients not cured by frontline therapy nor by second line autologous stem cell transplantation (ASCT), and patients with anaplastic large cell non-Hodgkin lymphoma (ALCL) who fail initial therapy.

HL is curable in the majority of patients, especially when diagnosed in earlier stages, where cure rates often exceed 90% and where the major clinical research questions focus on how little treatment is required to cure these patients and avoid late toxicities. For those patients with advanced stage HL cure rates are less but a majority is cured with regimens such as ABVD. For all HL patients, roughly 30% eventually relapse. When patients are not cured

with the standard upfront therapy, roughly half may still be cured with high dose chemotherapy and autologous stem cell transplantation (ASCT). Patients who further relapse despite ASCT have very short survivals (32% alive 5 years later) and are rarely cured. Treatment options are limited.

ALCL is a rare type of NHL (2,000/year diagnosed in USA) for which new treatments are also needed. Fewer than half the patients are alive and disease free three years after diagnosis. Those patients who have ALK-1 negative ALCL or high risk IPI status, despite ALK status, fare especially poorly. There is no standard therapy for relapsed or refractory ALCL. We usually treat these patients with ASCT but over 50% of patients relapse, most within 3 years. After ASCT for relapsed/refractory ALCL, the 5-year progression-free survival is 29% and the 5-year overall survival is 37%.

So for both of these groups of patients: HL refractory to our usual treatments and ALCL, we have been in desperate need for new, effective treatments, a so-called "unmet need" for patients and physicians.

Over 95% of HL and all of ALCL express CD30, a member of the tumor necrosis factor receptor superfamily, on their cell surfaces. Previous clinical trials using "naked" anti CD30 monoclonal antibodies have been ineffective.

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PHYSICIANS REPORT



A novel CD30 antibody was developed by Seattle Genetics whereby the CD30 antibody is conjugated by a protease-cleavable linker to the potent antimicrotubule agent, monomethyl auristatin E (MMAE). The drug, which is an antibody drug conjugate or ADC, known sequentially as SGN35, brentuximab Vedotin, and Adcetris, was FDA approved in the late summer of 2011. Brentuximab Vedotin is thought to work through the following mechanism: binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, then release of MMAE via proteolytic cleavage. MMAE binds to tubulin, disrupting the microtubule network within the cell thereby inducing cell cycle arrest, resulting in apoptotic death of the cells

Phase II pivotal trials in both disease demonstrated remarkable efficacy in these poor-risk patients. In HL 102 patients with a median of five prior therapies, all of whom had failed ASCT, the overall response rate was 73%, with half of those being complete responses. In ALCL, 58 patients were treated, the majority of whom were ALK-1 negative, and the overall response rate was 86% with a CR rate of about 60%.

Brentuximab Vedotin was rapidly approved based on these data.

At Colorado Blood Cancer Institute (CBCI), we have been part of many of the seminal and ongoing studies with Brentuximab Vedotin. One needs to be cognizant of peripheral, and rarely motor, neuropathy. The neuropathy is cumulative, primarily sensory and dose modifications or delays are often required.

There are a number of questions, which we need to answer regarding Brentuximab Vedotin: can it cure patients? What is the optimum length of treatment? What about combinations? Should we use it preemptively after transplant?

Ongoing clinical trials are evaluating the role of Brentuximab Vedotin as upfront treatment in advanced stage HL and

preliminary data were reported at ASH 2011 by Anas Younes with ABVD + Brentuximab Vedotin or AVD (no bleomycin) + Brentuximab Vedotin. Another trial in process and active at CBCI examines the role of Brentuximab Vedotin consolidation after ASCT. Manuscripts in press reveal efficacy for HL relapsing after allogeneic transplant. Research is just beginning with Brentuximab Vedotin in other types of NHL and solid tumors expressing CD30.

This is an exciting new therapy to have for the patients for whom we have been in need of options. We have at CBCI over the years been part and continue to be part of many of these Brentuximab Vedotin studies and are available to you for any questions you might have regarding your patients.

#### *Selected references from ASH 2011:*

**Brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma: A Phase 2 Study Update.** Ranjana H. Advani, Andrei R. Shustov, Pauline Brice, Nancy L. Bartlett, Joseph D. Rosenblatt, Tim Illidge, Jeffrey Matous, Radhakrishnan Ramchandren, Michelle A. Fanale, Joseph M. Connors, Yin Yang, Dana A. Kennedy, and Barbara Pro. ASH Annual Meeting Abstracts 2011 118:443

**Prolonged Treatment with Brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Hodgkin Lymphoma (HL) or Systemic Anaplastic Large Cell Lymphoma (sALCL).** Andres Forero-Torres, R. Brian Berryman, Ranjana H. Advani, Nancy L. Bartlett, Robert W. Chen, Michelle A. Fanale, Ajay K. Gopal, Owen A. O'Connor, Randal Olsheski, Scott E. Smith, Laurie E. Grove, and Jeffrey Matous. ASH Annual Meeting Abstracts 2011 118:3711

**Frontline Therapy with Brentuximab Vedotin Combined with ABVD or AVD in Patients with Newly Diagnosed Advanced Stage Hodgkin Lymphoma.** Anas Younes, Joseph M. Connors, Steven I. Park, Naomi N.H. Hunder, and Stephen M. Ansell. ASH Annual Meeting Abstracts 2011 118:955

## Systemic Sclerosis: Hematopoietic Cell Transplantation

### RICHARD NASH, MD

Hematopoietic (blood) cell transplantation (HCT) is a procedure that is now routinely used for treatment of hematological malignancies. The source of the blood stem cell can be from one's own blood (autologous) or from a donor (allogeneic). Both types of transplantation can have a profound effect on the immune system. After intensive chemotherapy followed by autologous HCT, depletion of autoreactive

immunologic memory has been observed. After allogeneic HCT, the autoreactive immune system is replaced by a donor-derived immune system without the predisposition to damage organs which were targets of the autoimmune disease.

Systemic sclerosis is a potentially life-threatening autoimmune disease which is characterized by a vasculopathy and fibrosis of skin and internal organs. Skin fibrosis (or scleroderma) if extensive may severely restrict movement and functional abilities. Heart, lung and kidney may fail as a result of the disease process. The gastrointestinal tract can also be extensively involved with marked dysfunction. Although immunosuppressive or immune modulating therapies are commonly used, none have been demonstrated to be a successful treatment for systemic sclerosis. Since no effective treatments had been

identified for systemic sclerosis, studies were initiated in the late 1990's to investigate the effectiveness of hematopoietic cell transplantation.

Several groups have now conducted pilot studies of high-dose immunosuppressive therapy (HDIT) followed by autologous HCT for patients with severe systemic sclerosis. Outcomes were thought to be promising. At 4 years after treatment, more than half of the patients were in remission, without progression of the disease and had not required any therapy since the transplant. A decrease in the extent of the scleroderma or skin re-modeling was observed. There was evidence for improvement in the vasculopathy as well. A randomized clinical trial with follow-up to 1 year showed that HDIT followed by autologous hematopoietic cell transplantation was much more effective than monthly doses of cyclophosphamide.

Two other randomized clinical trials with longer follow-up are either still following patients or in the process of analyzing data and have not reported their results yet.

The Colorado Blood Cancer Institute in collaboration with the Scleroderma clinic at the University of Colorado is now conducting a new clinical trial of HDIT followed by autologous HCT (STAT). This clinical trial will investigate transplanting patients earlier in the course of their disease and will also investigate ways of reducing the risk of disease relapse after transplant. We will also be opening a clinical trial of allogeneic HCT for severe systemic sclerosis to assess if this may be more effective and responses more durable than HDIT followed by autologous HCT.

## Nonmyeloablative Allogeneic Transplants for Older Patients with Hematological Malignancies

### PETER McSWEENEY, MD

Over the last 15 years so-called reduced intensity allogeneic transplants emerged from being an experimental form of transplantation into a broadly applied therapeutic modality. The treatment was developed to allow allogeneic transplants to be performed in older or otherwise medically less fit patients who wouldn't qualify for this type of treatment. Critical aspects of this therapy is the use of low-intensity better-tolerated transplant regimens and reliance on graft-versus-tumor effects to achieve the therapeutic goal of suppressing the patient's cancer. This therapy has been almost exclusively used in treating hematological malignancies where the host hematopoietic system is a good target for donor immune cell attack. While large randomized studies of this modality are still lacking, phase 2 studies have demonstrated

that potent antitumor effects accompany these transplants, predominantly demonstrated through induction and sustaining of remissions of high risk hematological malignancies.

A recent study analyzed results of this treatment for patients over 60 years of age with hematological malignancies – "Long-Term Outcomes Among Older Patients Following Nonmyeloablative Conditioning and Allogeneic Hematopoietic Cell Transplantation for Advanced Hematologic Malignancies" (Sorrer et al, JAMA, November 2, 2011). In this study, patients were enrolled from multiple centers including Colorado Blood Cancer Institute (CBCI) and two of our physicians; Dr. Peter McSweeney and Dr. Michael Maris were co-authors of the multicenter collaborative study which was led by investigators at the Fred Hutchinson Cancer Research Center in Seattle.

The study included 372 patients treated between 1998 and 2008 who were between 60-75 years old with hematological malignancies including acute and chronic leukemias, myelodysplastic syndromes, myeloproliferative diseases, Hodgkin and non-Hodgkin lymphoma and multiple myeloma. Patients were enrolled in prospective clinical trials of nonmyeloablative allogeneic transplantation at 18 collaborating institutions using conditioning immediately prior to transplant of low-dose total body irradiation with or without fludarabine. Transplants donors were related (n=184) or unrelated (n=188). Overall, 5-year cumulative incidences of non-relapse mortality and relapse were 27% and 41% respectively, with overall survivals and progression-free 5-year survivals of 35% and 32% respectively. Thus approximately a third of patients were alive without disease progression at 5 years after

their transplants. Outcomes were analyzed by 3 age groups: ages 60-64 years (n=218), 65-69 years (n=121) and > 69 years (n=33).

*(continued on page 4)*



## NONMYELOABLATIVE ALLOGENEIC *continued*

No statistically significant differences were found among these age groups in terms of relapse mortality, transplant mortality and overall survivals. Factors more strongly associated with adverse outcomes included inferior general health as measured by the hematopoietic cell transplantation co-morbidity index, use of mismatched donors and patients with advanced malignancy.

Patients enrolled on these studies have had malignancies associated with poor survival when treated with conventional treatment. A continued finding in these studies has been that transplants results using matched unrelated donors transplant result in similar outcomes to those with matched siblings indicating that the lack of a sibling shouldn't limit the application of these transplants. These findings support the idea that allogeneic transplants can be successfully used in patients beyond 60 years of age and in suitable candidates beyond 70 years of age. Further improvements are clearly still needed and should come from better methods for preventing and treating graft-versus-host disease and the addition of newer antitumor drugs to the transplant protocols.



Sarah Cannon in Collaboration with Colorado Blood Cancer Institute Present...

# 2011 ASH REVIEW

## Updates on the Treatment and Management of Hematologic Malignancies

Thursday, February 9, 2012, 5:30-9:00 PM  
Denver, Colorado

**5:30-9:00 pm**

Registration and Dinner Begin at **5:30 pm**

Educational Session Begins at **6:00 pm**

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**\*\*For more information on the conference and materials visit [bloodcancerinstitute.com](http://bloodcancerinstitute.com)**