Case Studies in Rare Lymphomas: Hodgkin Lymphoma and Systemic Anaplastic Large Cell Lymphoma

INTRODUCTION

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HODGKIN LYMPHOMA

Management Following Failure of Autologous Stem Cell Transplant
Joseph M. Connors, MD

HODGKIN LYMPHOMA

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Andreas Engert, MD

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Management Following Failure of One or More Combination Regimens
Steven M. Horwitz, MD

Webcast available at ASCOPost.com/lymphomaweb/
More than 400 oncologists, hematologists, pathologists, clinical scientists, and nurses attended the 2012 Pan Pacific Lymphoma Conference held in July 2012 at the Hyatt Regency Maui Resort & Spa in Hawaii. A special roundtable discussion on Case Studies in Rare Lymphomas was held in conjunction with the Conference and presented by The ASCO Post. You may view a webcast of this discussion at www.ASCOPost.com/lymphomaweb/

The roundtable discussion was moderated by James O. Armitage, MD, Professor, Department of Internal Medicine, Joe Shapiro Distinguished Chair of Oncology, University of Nebraska Medical Center in Omaha, and Editor-in-Chief of The ASCO Post. The discussion included presentations by Joseph M. Connors, MD, Clinical Director, Centre for Lymphoid Cancer, British Columbia Cancer Agency, University of British Columbia in Vancouver; Andreas Engert, MD, Chairman, German Hodgkin Study Group, Professor for Internal Medicine, University Hospital of Cologne in Germany; and Steven M. Horwitz, MD, Assistant Attending, Lymphoma Service, Memorial Sloan-Kettering Cancer Center in New York City.

During the program, panel members presented case studies of patients with Hodgkin lymphoma and systemic anaplastic large cell lymphoma and the treatment management options for each patient. Each session was followed by a Q&A discussion among the panelists.

This special supplement is a companion piece to a webcast presentation, including the cases presented and faculty discussion. You may view the entire presentation and complete slides by visiting www.ASCOPost.com/lymphomaweb/

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When considering the management of a patient whose Hodgkin lymphoma has relapsed despite high dose chemoradiotherapy and autologous hematopoietic stem cell transplantation, it is useful to consider three distinct scenarios, as described in the following case summaries.

Patient 1

Patient 1 is a 26-year-old man who presented with night sweats, fevers, and cough. On examination, he was found to have palpable bilateral supraclavicular lymphadenopathy and wheezing but no other localizing symptoms. Open lymph node biopsy of a supraclavicular node revealed nodular sclerosing Hodgkin lymphoma. CT and FDG-PET demonstrated abnormally enlarged lymph nodes in the supraclavicular fossae, mediastinum, and retrocrural and retroperitoneal regions bilaterally but no other abnormal masses. The largest lymph node mass was 6 cm in greatest diameter.

For his stage IIIB classical Hodgkin lymphoma, the patient was treated with six cycles of standard ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine), after which both CT and PET scanning were negative, indicating a complete response. Four months later, the patient noted recurrent night sweats and detected supraclavicular lymphadenopathy. Biopsy confirmed relapsed Hodgkin lymphoma, and CT/PET demonstrated recurrence in the neck and mediastinum. The patient was then treated with two cycles of GDP chemotherapy (gemcitabine, dexamethasone, cisplatin) with good response, followed by high-dose BEAM chemotherapy (carmustine [BiCNU], etoposide, cytarabine, melphalan) and autologous stem cell transplant, after which CT/PET scanning was once again negative. Six months later, night sweats recurred, and relapse in the neck and mediastinal nodes could be seen on CT/PET scanning.

Patient 2

Patient 2 had a similar initial presentation (stage IIIB, nodular sclerosing Hodgkin lymphoma) and was treated with six cycles of ABVD; however, postchemotherapy CT/PET remained positive for disease in the neck and mediastinum, and involved-field radiation (3,500 cGy in 20 fractions) to the abnormal nodes in the neck and mediastinum was added. Nine months later, the Hodgkin lymphoma recurred within the previously irradiated lymph nodes, prompting treatment with two cycles of GDP followed by high-dose chemotherapy and autologous stem cell transplant, but in another 9 months, a second in-field relapse occurred.

Patient 3

Patient 3 presented with bulky (> 10 cm) stage IIB nodular sclerosing Hodgkin lymphoma, but his disease progressed during the fifth cycle of ABVD. Despite subsequent treatment with GDP, high-dose BEAM, autologous stem cell transplant, and involved-field radiation to the neck and mediastinum, the lymphoma once again recurred in-field in the neck and mediastinum.

Discussion

These three patients illustrate the three distinct scenarios that may unfold on the way to re-emergence of Hodgkin lymphoma after autologous stem cell transplant. Patient 1 had node-only relapse of previously unirradiated node-only classical Hodgkin lymphoma after transplant and is potentially curable with extended-field radiation with or without MOPP-type chemotherapy (mechlorethamine, vincristine, procarbazine, prednisone). Patient 2 had chemotherapy-sensitive late relapse (> 6 months after autologous stem cell transplant) of Hodgkin lymphoma that had not been primarily resistant to the original ABVD plus involved-field radiotherapy. Preliminary data indicate such a patient may...
be curable with further chemotherapy followed by allogeneic stem cell transplant, but this technique remains experimental and is best offered within the context of a clinical trial. Patient 3 had ABVD-resistant Hodgkin lymphoma and experienced rapid relapse despite high-dose chemotherapy, stem cell transplant, and involved-field radiotherapy.

This latter situation—relapse of Hodgkin lymphoma after autologous transplant in a manner not approachable with potentially curative radiation or allogeneic transplant—is the most common one encountered (~70% of patients) and requires planned management aimed at minimizing toxicity, controlling symptoms, and ensuring the best possible quality of life even though the Hodgkin lymphoma cannot be cured (Table 1). This can usually be best accomplished by judicious use of involved-field radiation for localized symptoms such as a painful mass or bone lesion and single-agent chemotherapy. Reliance on single-agent chemotherapy eliminates concerns that arise when multiple agents are used and cause toxicity, although only one of the agents may be having a beneficial effect.

Desirable characteristics of the single agent include a high response rate, minimal toxicity, durability of response, convenient scheduling, and oral administration. If possible, the single agent chosen should avoid difficult-to-control nausea, marked myelotoxicity, hair loss, or need for frequent administration. Durability of response is particularly desirable because it allows treatment-free intervals.

No single agent possesses all of those useful characteristics, but vinblastine, gemcitabine, and lomustine are often helpful and well tolerated. Preliminary data indicate that bendamustine (Treanda) may also prove useful for this purpose, but more experience is needed (and myelotoxicity can be a major issue). More recently, brentuximab vedotin (Adcetris), an anti-CD30 antibody-drug conjugate, has been shown to be very well tolerated and highly effective for palliation of recurrent Hodgkin lymphoma and should be strongly considered for this use. 1-5

### Table 1: Treatment options for Hodgkin lymphoma in relapse after autologous stem cell transplant in cases where potentially curative radiation or allogeneic transplant is not possible.

<table>
<thead>
<tr>
<th>Agent</th>
<th>ORR (%)</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinblastine</td>
<td>~60%</td>
<td>Few months</td>
<td>≤1-2 weekly, little toxicity</td>
</tr>
<tr>
<td>Lomustine</td>
<td>~50%</td>
<td>Few months</td>
<td>Oral, q-4-6 weeks, myelotoxicity</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>~40%</td>
<td>Few months</td>
<td>Oral, q-5-6 days, myelotoxicity</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>~70%</td>
<td>~5-6 months</td>
<td>Oral, q-4-6 days</td>
</tr>
<tr>
<td>Brentuximab</td>
<td>~75%</td>
<td>6-12 months</td>
<td>~5-6 weeks, marked hair loss, excellent evidence base</td>
</tr>
</tbody>
</table>

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**Suggested Readings**

As oncologists, we face many challenges. The most difficult is when you say to a patient with a disease everybody expects will be cured, ‘It is not worth trying to do that. It is time to worry about keeping you as well as possible for as long as possible but to quit taking chances.’ When do you think you should do that, and how do you tell the patient? I would like to know how all of you do that.

I often see the choice made to use multiagent chemotherapy to manage what has become an incurable condition. The difficulty there is that the patient experiences all the toxicity of all the agents, but maybe profits from improvement brought about by only one or two of those agents. And if you combine drugs, you have to compromise the doses of many of those drugs. I really do think it preferable to settle upon optimizing the dosing and scheduling of one agent, understanding whether it is working or not, and using it to maximum utility.

But to return to your question, I think that this is the point at which you have to thoroughly impress upon patients that just because you are changing the aim of treatment, it does not mean you are changing your deep commitment to their care.

As oncologists, we face many challenges. The most difficult is when you say to a patient with a disease everybody expects will be cured, ‘It is not worth trying to do that. It is time to worry about keeping you as well as possible for as long as possible but to quit taking chances.’

— James O. Armitage, MD

Dr. Armitage: What do the rest of you think?

First, there are quite a few differences among these patients. Some patients relapse very early after transplant, have a very poor prognosis that is comparable to pancreatic cancer, for instance; others relapse a year or more later and have a much better prognosis, although in the past, these patients usually were regarded as incurable. Some patients (but not many) are being taken to allogeneic transplant. There is a good chance that these patients will live for many years, and it would be too early to approach them when they relapse 2 years after transplant and say, “Well, you are going to die soon”—that is certainly not appropriate.

Others have gone through many rounds of treatment and feel themselves that they will not have too many more rounds. These are the candidates we speak to, explaining that what we do is aimed at improving their quality of life so that they can do what they like to do as much as possible, and that we have to find the balance between reducing disease activity and keeping them fit. That is something most of them want and understand. In a way, the patient is a partner in going to bring their way. Reassuring them that many patients in this situation have excellent quality of life for months to years if they are properly managed with appropriate therapies.

You have to impress upon patients that just because you are changing the aim of treatment, it does not mean you are changing your deep commitment to their care.

— Joseph M. Connors, MD
that process; very often patients feel much more and know much more than we doctors think they do.

Dr. Horwitz: These are hard conversations, but we have them often. Frequently, it first comes up in the setting of when patients relapse and they are referred to autologous stem cell transplantation. Many patients ask at that point, “What if this does not work? What happens then?” That is often the first time the possibility of not being cured arises.

If a patient continues to relapse several times, we make these decisions very individualized. The hard conversation often arises in the setting of an allogeneic stem cell transplant consult, when we’re explaining how that works and what those results are. Sometimes you can come together on a plan, but it is very difficult transitioning people to accept the idea of not being cured.

We often use investigational therapies in this setting, not only to look at new therapies but also as a way to avoid having that conversation or to minimize the anxiety, because you can get excited about something new and different.

Dr. Armitage: Usually in a situation like this, when things are not going well, we assume that the new symptom or the new image abnormality represents the disease we are treating. There are probably sometimes when you should not be making that assumption and you better be thinking about doing a biopsy. So, what are the hints that this apparent treatment failure really is not a failure and you had better be working it out?

Dr. Connors: It is very important to be skeptical about the explanations we provide for any of these findings. When the disease has come back and caused exactly the same problems or is in exactly the same place, you are on somewhat safer ground. As soon as anything is atypical, does not match up, you should question it, and if in any doubt whatsoever, you should think about biopsying the disease for two reasons.

First of all, it could be nonmalignant or it could be a different malignancy. It is important to remember that some of these patients relapse with non-Hodgkin lymphomas, or sometimes other cancers appear at this point, and you would not want to make the wrong assumption. So a biopsy may be exactly the right thing to guide the decision-making.
This is a case report of a 23-year-old female patient who was diagnosed with Hodgkin lymphoma in January 2009. She received two cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and had progressive disease. She was therefore switched to an escalated BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine) and had a short temporary partial remission.

**Primary Progressive Hodgkin Lymphoma**

The question is, how do we best treat patients with primary progressive Hodgkin lymphoma? This group of patients has a rather poor prognosis, with 5-year tumor control of less than 20% and overall survival of less than 30% (Fig. 1). Importantly, the most effective treatment for these patients is high-dose chemotherapy, even in a situation of disease refractory to first-line regimens. Most groups use a non–cross-resistant regimen to mobilize stem cells, such as DHAP (dexamethasone, high-dose cytarabine, cisplatin), ICE (ifosfamide, carboplatin, etoposide), or IGEV (ifosfamide, gemcitabine, vinorelbine). In most cases the high-dose chemotherapy regimen used is BEAM (carmustine [BiCNU], etoposide, cytarabine, melphalan).

Our patient had one cycle of ICE with progressive disease again and was followed with two cycles of DHAP including stem cell mobilization. High-dose BEAM chemotherapy was administered and stem cell transplant was performed in September 2009, and this was followed by additional radiotherapy. Unfortunately, the patient experienced another relapse/progressive disease in early 2010. This is when she presented at our center for further treatment.

**Prognosis in Patients Who Relapse following High-dose Chemotherapy**

From a large international collaborative project, data have emerged on the prognosis of patients relapsing after high-dose chemotherapy. Those relapsing within 3 months after transplant have a par-
particularly dismal prognosis, with an overall survival of approximately 6 months. Most of these patients are treated with palliative intent, receiving either single-agent chemotherapy or best supportive care. Only patients with a suitable donor and very good response to treatment might be considered candidates for an allogeneic transplant. However, very few of these patients refractory to high-dose chemotherapy were successfully allotransplanted.

Thus, there is a strong need for alternative agents with different modes of action. To this end, the new anti-CD30 antibody-drug conjugate brentuximab vedotin (Adcetris) (Fig. 2) has shown extremely impressive results in both phase I and phase II studies. In patients with relapsed and refractory Hodgkin lymphoma who had received prior high-dose chemotherapy and autologous stem cell transplant, the response rate was 75% overall, with 34% of these patients achieving complete remission. The tolerability was excellent, with only a few patients experiencing clinically relevant neutropenia. Relevant peripheral neuropathy (grade 3) was observed in 9% of patients; there was no grade 4 peripheral neuropathy.

At the time the 23-year old female patient presented at our center, brentuximab vedotin became available in a named patient program. The patient received four cycles of treatment and responded extremely well (Fig. 3). Subsequently, she received a haploid allogeneic transplant and achieved a complete remission.

This is a remarkable case of a patient with a very aggressively growing tumor that is not responding to any chemotherapy or radiotherapy. She responded very well to brentuximab vedotin and achieved nearly a complete remission with this drug, and that enabled her to undergo an allogeneic transplant.

References

Fig. 2: Brentuximab vedotin, or SGN-35, is an antibody-drug conjugate. The antibody is anti-CD30. The chemotherapeutic drug is the antitubulin agent monomethyl auristatin E (MMAE). They are joined together by a protease-cleavable linker that is stable in plasma, but degraded by lysosomal enzymes. This conjugate binds to CD30, which is expressed on the surface of Hodgkin lymphoma cells. It then gets internalized and traffics to lysosome, where the MMAE is released. MMAE then disrupts the microtubule network, leading to cell-cycle arrest and apoptosis.

Fig. 3: A 23-year-old woman with relapsed and refractory Hodgkin lymphoma before and after four cycles of therapy with brentuximab vedotin.
**Dr. Armitage:** It is no surprise that brentuximab vedotin is really an exciting agent, and it gives us a new opportunity in treating classical Hodgkin lymphoma. What if this person Dr. Engert just presented was at the same point with nodular lymphocyte-predominant lymphoma and no CD30 positivity. What would you do in that case?

**Dr. Engert:** Patients differ in terms of their immunophenotype, and some do not express much CD30, but they do express CD20, an antigen that is basically expressed on Hodgkin lymphoma cells. So these tumors are strongly CD20-positive, and rituximab (Rituxan) or other antibodies against CD20 have been used successfully in these patients.

**Dr. Armitage:** When a patient with classical Hodgkin lymphoma goes into remission in a timely way after brentuximab vedotin, when should you just monitor that response and hope that the patient is one of those who appear to be cured? When is it better to do that, and when is it better to take other chances?

**Dr. Connors:** My perspective is that we may be seeing our whole approach to treating the disease change with the availability of this new agent. Because in the case of a patient with primary progressive disease, until now, we did not have a way to achieve such good disease control that an allotransplant would be an attractive option. Brentuximab may be a game-changing intervention with a greater depth of response that makes that intervention available.

“*In the case of a patient with primary progressive disease, until now, we did not have a way to achieve such good disease control that an allotransplant would be an attractive option. [Brentuximab] may be a game-changing intervention with a greater depth of response that makes that intervention available.*”

— Joseph M. Connors, MD

**Dr. Armitage:** Are there patients for whom you would not do such a thing—for example, a 50-year-old patient with a mismatched unrelated donor—where you would either take the complete response and hope that it lasts or give ongoing brentuximab?

**Dr. Horwitz:** In some ways, you can base that decision on a patient’s disease course. There are people who have more of a chronic Hodgkin lymphoma and respond to one treatment after another. With these patients, you have a sense of confidence that if you lose that remission, you could get another one. These are patients you can keep retreating, and I think in these people, there is sometimes a temptation to spare them the toxicity and the unknown risk of allotransplantation.

In the case of the patient described, however, you would be very surprised to achieve a remission from anything. In this case, you would be apprehensive about letting that remission pass without performing an allotransplant.

**Dr. Connors:** This patient needs to have an honest appraisal of both the likelihood that an allotransplant is going to work and the potential toxicity involved. I hope the story turns out happy in the end, but there is still a very high chance she is going to relapse again, and all you can do is offer the best opportunity for remission.
This is a case of a 49-year-old woman who developed an enlarged right axillary lymph node. The woman had noticed some discomfort under her right arm, which she initially believed was an ingrown hair. Over a month or two, this grew to the size of a chickpea. The woman’s primary medical doctor ordered a mammogram, which was unremarkable in the breast but confirmed a 1.5-cm right axillary node enlargement. A CT scan of the chest showed the right axillary node as well as some subpectoral lymphadenopathy and a lung nodule. An excisional right axillary node biopsy was performed and showed ALK-negative anaplastic large cell lymphoma. At this point, the woman was referred to our center.

**Workup**

A PET/CT scan showed increased FDG uptake in the remaining subpectoral node as well as the lung nodule. Fine-needle aspiration of the lung nodule showed an anaplastic large cell lymphoma, with large CD30-positive T cells. A bone marrow biopsy was negative. Her lactate dehydrogenase (LDH) level was elevated. This was a young woman with stage IV disease, high LDH, and an International Prognostic Index of 2.

In general, we think of ALK-negative anaplastic large cell lymphoma as a fairly aggressive, poor-prognosis lymphoma that we generally treat more aggressively than ALK-positive anaplastic large cell lymphoma (Fig. 1). CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) is probably the most commonly used regimen in this setting. There is a sense that etoposide in addition to CHOP, or CHOEP, adds benefit. It was recommended that this patient receive CHOEP followed by an autologous stem cell transplant.

The woman was started on CHOEP and tolerated this reasonably well. She initially started on an every-2-week schedule, but it was extended to every 3 weeks due to hematologic toxicity. Repeat staging after four cycles showed a PET-negative complete response. Her stem cells were collected, she proceeded to high-dose therapy and autologous stem cell transplant, and she did well. However, routine imaging at 1 year showed new lymphadenopathy and biopsy-confirmed recurrent disease.

**Discussion**

At this point, patients with T-cell lymphoma or anaplastic large cell lymphoma are left with a little bit of a conundrum in the sense that we really do not have strong data to guide us. Two of the drugs approved in this setting, pralatrexate (Folotyn) and romidepsin (Istodax), were studied in relatively large phase II studies, with response rates of 25% to 30%. In a minority of patients who respond, there is some durability of response if you keep patients on therapy—sometimes a year or more—but re-
ally not a sense that this is a curative approach. A handful of other drugs (gemcitabine, bendamustine [Treanda], lenalidomide [Revlimid]) have been looked at in smaller phase II studies and have shown some activity.

The novel agent brentuximab vedotin (Adcetris) targets CD30. Hodgkin lymphoma and anaplastic large cell lymphoma are probably the strongest, most uniform CD30-expressing lymphomas, and it looks like brentuximab vedotin hits that target very well. At least the phase II data we have in anaplastic large cell lymphoma are quite impressive (Fig. 2).

The study shown in Fig. 2 led to the approval of brentuximab for relapsed anaplastic large cell lymphoma. The overall response rate was 86%, more than half of those patients with relapsed disease had complete responses, and durability was on average about a year.

**Brentuximab Vedotin in Relapsed ALCL**

<table>
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<tr>
<th>Measure</th>
<th>Response (N = 58)</th>
<th>95% CI</th>
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<tr>
<td>Objective response rate, %</td>
<td>86</td>
<td>74.6 to 93.9</td>
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<tr>
<td>CR rate</td>
<td>57</td>
<td>43.2 to 69.8</td>
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<tr>
<td>Partial remission rate</td>
<td>29</td>
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<tr>
<td>Stable disease, %</td>
<td>3</td>
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<tr>
<td>Progressive disease, %</td>
<td>5</td>
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<tr>
<td>Histologically ineligible, %</td>
<td>3</td>
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<tr>
<td>Not evaluable, %</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Median duration of objective response, months</td>
<td>12.6</td>
<td>5.7 to NE</td>
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<tr>
<td>Median duration of response in patients with CR, months</td>
<td>13.2</td>
<td>10.8 to NE</td>
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<tr>
<td>Median progression-free survival, months</td>
<td>13.3</td>
<td>8.9 to NE</td>
</tr>
<tr>
<td>Median overall survival, months</td>
<td>Not reached</td>
<td>14.6 to NE</td>
</tr>
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</table>

Pro B et al. JCO 2012;30:2190-2196

Fig. 2: This study led to the approval of brentuximab for relapsed anaplastic large cell lymphoma. The overall response rate was 86%, more than half of those patients with relapsed disease had complete responses, and durability was on average about a year.

**Management of Systemic Anaplastic Large Cell Lymphoma following Failure of One or More Combination Regimens**

**KEY POINTS**

- The addition of the agent etoposide to the chemotherapy regimen CHOP appears to improve overall survival in ALK-positive anaplastic large cell lymphoma patients.
- In a phase II study of brentuximab vedotin in relapsed anaplastic large cell lymphoma patients, the overall response rate was 86%, more than 50% of patients experienced a complete response, and median progression-free survival was 13.3 months.
- In subsets of ALK-negative anaplastic large cell lymphoma patients, brentuximab vedotin had significantly higher response rates than romidepsin and pralatrexate in phase II studies.

**Suggested Readings**

**Faculty Q&A Discussion**

**Dr. Armitage:** For ALK-negative anaplastic large cell lymphoma, brentuximab vedotin is the best thing we have to deal with patients with recurrent disease, and who knows where it will end up in primary therapy. But if the patient is ALK-positive, there is a potential for crizotinib (Xalkori) to make a big difference, even though it has been developed for lung cancer. Have you had any experience with crizotinib?

**Dr. Horwitz:** No. We have not used crizotinib. ALK-positive disease is often cured, and our bias is that patients fare better with second-line therapy and stem cell transplant, but I do not think we really know. Our sense is that ALK-positive disease is more chemosensitive, so we have not used the drug. There have been a couple of anecdotes and small series presented at meetings, about a couple of adult patients who responded. And there was a small group of patients in a pediatric ALK-expressing tumor study presented at ASCO [2012 Annual Meeting]. Six out of seven or eight patients responded, so it looks very promising. Those are rare patients, but I think crizotinib is something that could be used here. I do not think we really know the durability nor how to incorporate that into curative therapy yet, but the agent probably is very active.

**Dr. Armitage:** Dr. Horwitz, what is your sense of the durability of responses induced by brentuximab?

**Dr. Horwitz:** It is hard to say. A number of the patients in the phase II study went on to transplant. I think a lot of my bias comes from the fact that if the patient has relapsed after combination chemotherapy, the likelihood that one drug will be curative is probably low. So if a curative approach is available, then we often take that approach.

Among the patients who had a complete response and did not undergo transplant, a number of those still have ongoing remissions, some of them have been retreated or are on continuous therapy, and some of them have been off therapy. The numbers get pretty small, but there is probably a subset of patients who have pretty good durability.

For the patients who did not have a complete response—so their durability is probably quite short—with the data we have now, my advice is that it probably makes sense to move on to something else.

**Dr. Armitage:** The big question right now is, can we cure these patients eventually with brentuximab alone? Some patients have been on treatment for a year or longer. Alternatively, should they undergo allogeneic transplantation or autologous transplantation if they had not had an autologous transplantation previously? We don’t have the answers to these questions right now, but these are the issues we have to address in the future.

**Dr. Connors:** The natural experiment is playing out, because there will be patients for whom, either through choice or lack of available donors, the last treatment they received is brentuximab. If, in a year or two or more, we see that they are not relapsing, then we have our proof in hand. But it would probably be a surprise to all of us if we suddenly cured such an otherwise treatment-resistant disease with a single agent. So we better remain open-minded about it.

**Dr. Armitage:** Now we are talking about odd situations, but there are some people with cutaneous anaplastic large cell lymphoma who keep relapsing even though you can treat each one with radiotherapy or something else easily. There are people with lymphomatoid papulosis in whom treatment is challenging because the disease is continuously active. Have you treated any of those people with brentuximab, since they both express CD30?

**Dr. Horwitz:** We have, as part of a study. We think...
about primary cutaneous anaplastic large cell lymphoma as indolent, and lymphomatoid papulosis was spontaneously regressing, but people can get really symptomatic disease. We have treated two people with lymphomatoid papulosis using brentuximab vedotin as part of a study. Both responded, though the durability was short. We have probably treated three people with primary cutaneous anaplastic large cell lymphoma who then subsequently developed nodal disease. So, treating patients in that setting, two had good responses, although with relapses in the skin. My sense right now is that it is too early to say, but it probably is not curative in those chronically relapsing populations, at least not off therapy.

**Q** Dr. Armitage: Dr. Connors, Dr. Engert, do you have anything to add about these challenging situations?

**A** Dr. Engert: One open question is, how do patients fare, for example, those with Hodgkin lymphoma, when they have not had a transplant before? Because these were the patients who were not included in the pivotal study, and there were discussions in the United States and also in Europe as to whether the drug should be used in these individuals.

We collected 16 of these patients who were either too old or too sick for transplant, and we observed quite an encouraging response rate, allowing 6 of these 16 to go to autotransplant and stay in remission for at least until now. So that is a very interesting area, as is the issue of elderly patients who cannot receive transplant at all if they relapse.

**A** Dr. Connors: Conceptually, I think a transplant-ineligible patient is in just as much trouble when his disease relapses after primary therapy as he would be when relapsing after a transplant. There are not a lot of reliably curative options on the table, so I think that exploring the use of brentuximab in that population is going to be very rewarding.

**Q** Dr. Armitage: Dr. Horwitz, do you have a last word?

**A** Dr. Horwitz: One of the things we are learning as we are looking at this drug in CD30-expressing T-cell lymphoma is that there is a lot of variability in terms of expression, and in terms of different compartments being positive and negative. For example, we see a lot of negativity in bone marrow.

We have a very exciting drug that hits this target, and there is still a lot to learn about how we are interpreting that target, how much expression is needed, and how we look for that.
## Glossary of Drug Regimens Mentioned in this Supplement

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
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<td><strong>ABVD</strong></td>
<td>Doxorubicin, bleomycin, vinblastine, dacarbazine</td>
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<tr>
<td><strong>BEACOPP</strong></td>
<td>Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone</td>
</tr>
<tr>
<td><strong>BEAM</strong></td>
<td>Carmustine, etoposide, cytarabine, melphalan</td>
</tr>
<tr>
<td><strong>CHOEP</strong></td>
<td>Cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone</td>
</tr>
<tr>
<td><strong>CHOP</strong></td>
<td>Cyclophosphamide, doxorubicin, vincristine, prednisone</td>
</tr>
<tr>
<td><strong>DHAP</strong></td>
<td>Dexamethasone, cisplatin, cytarabine</td>
</tr>
<tr>
<td><strong>ESHAP</strong></td>
<td>Etoposide, methylprednisolone, cisplatin, cytarabine</td>
</tr>
<tr>
<td><strong>GDP</strong></td>
<td>Gemcitabine, dexamethasone, cisplatin</td>
</tr>
<tr>
<td><strong>ICE</strong></td>
<td>Ifosfamide, carboplatin, etoposide</td>
</tr>
</tbody>
</table>

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**A Webcast Presentation, from The ASCO Post**

To view the complete webcast of “Case Studies in Rare Lymphomas,” visit [ASCOPost.com/lymphomaweb/](http://ASCOPost.com/lymphomaweb/) or use your smart phone to connect by scanning the QR code on this page.
Save the Date

Hematology-Oncology Meetings, 2012–2014

September 14-15, 2012
NCCN 7th Annual Congress
Hematologic Malignancies
New York Marriott Marquis • New York, New York
http://www.nccn.org/professionals/meetings/hematological/default.asp

October 25-27, 2012
Lymphoma & Myeloma 2012: An International Congress on Hematologic Malignancies
Waldorf Astoria • New York, New York
http://www.lymphomaandmyeloma.com/2012/index.asp

December 8-11, 2012
2012 ASH Annual Meeting and Exposition
Georgia World Congress Center • Atlanta, GA
http://www.hematology.org/Meetings/Annual-Meeting/

June 19-22, 2013
12th International Conference on Malignant Lymphoma
Palazzo dei Congressi • Lugano, Switzerland
http://www.lymphicon.ch

October 12-15, 2013
9th International Symposium on Hodgkin Lymphoma
Cologne, Germany
https://www.hodgkinsymposium.org/

July 21-25, 2014
2014 Pan Pacific Lymphoma Conference
The Fairmont Orchid • Kohala Coast, Hawaii
http://www.unmc.edu/cce/panpacific/