Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

April 2011 www.clinicaladvances.com Volume 9, Issue 4, Supplement 9

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Peripheral T-Cell Lymphoma: A Case-Based Discussion of Recent Advances in Patient Management

Abstract

Peripheral T-cell lymphomas (PTCLs) are relatively rare, and data from large, comparative studies are limited. There are several histologic subtypes, which can be difficult to distinguish. Prognosis and management approaches can vary according to subtype. The standard management for PTCL patients is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens. Most patients will respond to CHOP, but a common drawback is the limited durability of response. Several recent trials have examined whether the addition of agents such as etoposide, alemtuzumab, and denileukin diftitox to CHOP can improve outcome. Data appear to suggest that such additions provide only a small amount of benefit, which may be limited to patients who are younger or who have a better prognosis. The newer agent pralatrexate may be beneficial, including when a fast remission is needed prior to a stem cell transplant. Upfront transplants are often used in patients in first remission. In this case-based discussion, Drs. Franco and Popplewell focus on the management of several PTCL subtypes: PTCL-not otherwise specified (PTCL-NOS), PTCL with cutaneous involvement, and angioimmunoblastic lymphoma (AITL).

Supported through funding from Allos Therapeutics, Inc.

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Case Presentations

Carlos M. Franco, MD

Case 1

The first case was a 54-year-old man in apparent good health. His prior medical history was essentially unrevealing, with the exception of a hernia repair, which occurred 2 years prior. The patient was a nonsmoker with no history of alcohol abuse. He had no medication allergies, and he was not on any medications at the time of presentation. He had a family history of melanoma and head and neck cancer.

He complained of pain in the lower left extremity, describing it as a sciatic-type pain that traveled down from the lower left back to the leg; this leg was also swollen. This pain prompted him to see his primary care physician, who used an ultrasound to rule out deep venous thrombosis. On the ultrasound, the physician observed an enlarged lymph node in the left groin. Upon examination, it was discovered that this lymph node was somewhat tender. The patient was treated with antibiotics, but the lymph node area did not improve, so he underwent further evaluation. Computed tomography (CT) scan revealed stage 3 adenopathy, with adenopathy above the diaphragm. This finding prompted a hematology/oncology referral.

The patient presented to my office in July 2009, at which time a complete physical examination was performed and imaging studies were taken (Figures 1 and 2). The examination was unremarkable, with the exception of an enlarged (approximately 3 cm) lymph node in the left inguinal area that was slightly tender. His left lower extremity was swollen, but he had no redness or calf tenderness, and there was no palpable cord. At the time, he had no complaints of fever, night sweats, weight loss, or infections. His laboratory results revealed a normal differential biochemical profile, a beta-2 microglobulin of 3.4 mg/L, and an elevated C-reactive protein level of 5 mg/L. The patient had evidence of slight leukocytosis (11,000 cells/mL, 63% granulocytes, 28% lymphocytes), an elevated erythrocyte sedimentation rate (28 mm/hr), and a high lactose dehydrogenase (LDH; 512 IU/L). A serum protein electrophoresis test was normal, as was the patient's level of uric acid (6.8 mg/dL). Positron emission tomography (PET)/CT showed retroperitoneal and mediastinal adenopathy as well as inguinal adenopathy. After a biopsy of the left inguinal lymph node, it was determined that the patient had anaplastic lymphoma kinase (ALK)-negative peripheral T-cell lymphoma (PTCL); a bone marrow biopsy was negative for lymphoma.

At this point, I discussed treatment options with the patient. I told him about my previous success using the

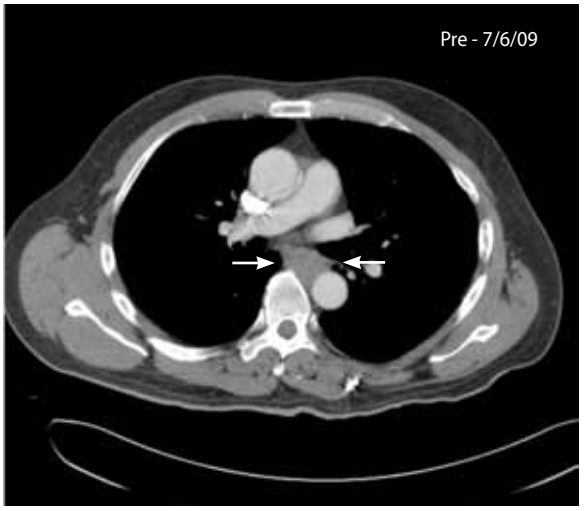

Figure 1. This scan shows the paraesophageal lymph node, before treatment.

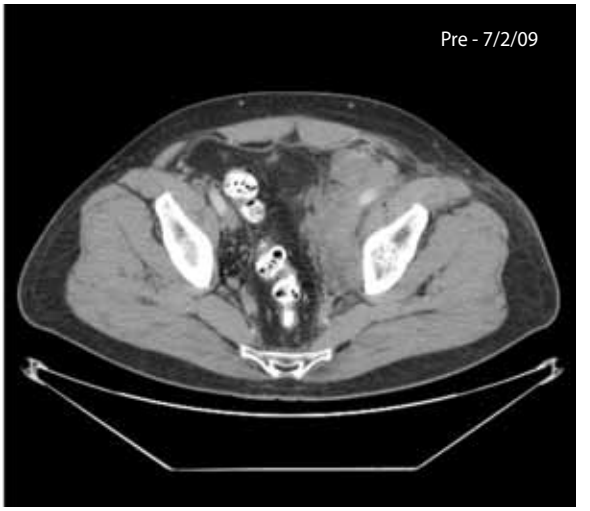

Figure 2. This scan shows the left external iliac lymph node, before treatment.

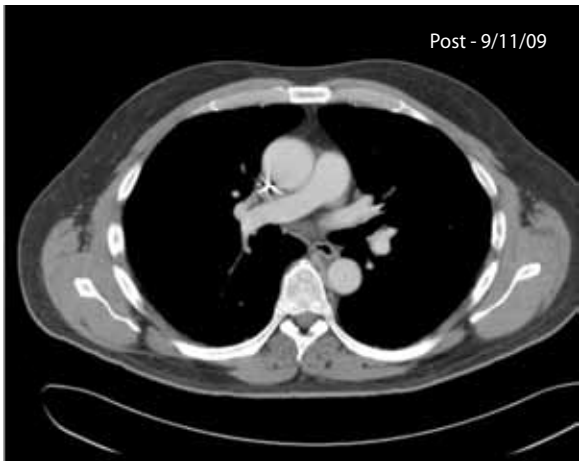

Figure 3. This scan shows the paraesophageal lymph node, after treatment.

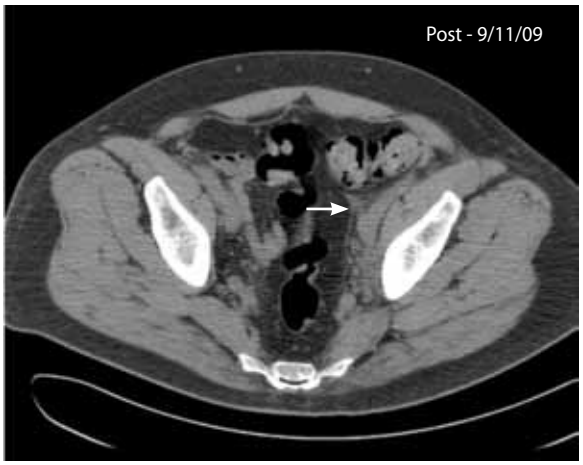

Figure 4. This scan shows the left external iliac lymph node, after treatment.

polychemotherapy regimen ProMACE-CytaBOM (consisting of cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate, and prednisone), which is active in aggressive B-cell lymphomas.[1] As has previously been reported by Fisher and shown by the Southwest Oncology Group, no intensive chemotherapy regimen (including ProMACE-CytaBOM) is superior to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in aggressive B-cell non-Hodgkin lymphoma.[2] However, I do not think these data can necessarily be applied to PTCL; in fact, the longest surviving PTCL patients I have treated received ProMACE-CytaBOM in the early 1990s. After further discussing the case with a transplant specialist at our institution, we decided to treat the patient with dose-dense CHOP because this regimen is well tolerated and can be completed sooner than conventional CHOP. Dose-dense CHOP was followed immediately by stem cell transplant (SCT) because of the patient's poor-prognosis ALK-negative disease.

The patient tolerated dose-dense CHOP very well, and he achieved complete remission by the final cycle. A PET/CT scan was negative (Figures 3 and 4), and he therefore underwent autologous SCT at the end of February 2010. He had no major complications from the SCT and did well for 3.5 months. However, he presented to my office after he noticed one morning that his glasses did not fit due to swelling of his left temporal area. A physical examination showed he had subcutaneous nodules in the chest wall and scalp. A CT scan revealed adenopathy in the mediastinum; PET showed multiple areas of soft tissue and muscle disease throughout the body, with subcutaneous nodules, infiltration into some muscle areas, and abnormal uptake in the mediastinum and hilar regions as well as the mesenteric lymph nodes. Overall, the imaging studies confirmed subcutaneous disease, with evidence of disease deep in some muscle areas, as well as adenopathy.

During a meeting with the same transplant team that performed the first SCT, multiple treatment options were presented to the patient. These included ifosfamide, carboplatin, and etoposide (ICE) chemotherapy or single-agent pralatrexate therapy; additionally, the need to find an allogeneic stem cell donor was discussed. During the donor search, the patient initiated a 6-week course of pralatrexate in mid-July 2010, to which he displayed excellent tolerance with no need for dose reduction or dose interruption. He was able to continue working during treatment. He achieved a complete response after the pralatrexate courses were complete. A spinal tap performed as part of a pre-allogeneic SCT evaluation showed monoclonal T cells in the spinal fluid. This finding prompted the initiation of a second course of pralatrexate, in addition to methotrexate delivered intrathecally twice-weekly, which proved to be too toxic. The patient developed severe mucositis, which was attributed to the combination of pralatrexate and methotrexate. The mucositis was treated with a magic mouthwash formulation. After 4 intrathecal methotrexate injections, his cerebral spinal fluid (CSF) was still positive for T cells by flow cytometry. The patient was then switched to cytarabine liposome injection. After a second injection, he began to receive pralatrexate. He went into systemic remission quickly with one 6-week cycle of pralatrexate, which has been well tolerated. He received 2 more 6-week cycles while waiting for allogeneic transplant, and he remains in remission. His CSF is finally negative by cytology and flow cytometry, after 4 injections of intrathecal methotrexate followed by 6 injections of intrathecal cytarabine liposome injection. He is scheduled for high-dose chemotherapy and allogeneic bone marrow transplant.

Discussion

Leslie L. Popplewell, MD You mentioned that the patient had ALK-negative PTCL. Was the lymphoma diagnosed as anaplastic large cell lymphoma (ALCL) or PTCL-NOS?

Carlos M. Franco, MD At our institution, he was diagnosed with PTCL-NOS, which was confirmed by a second opinion.

Leslie L. Popplewell, MD This is a very interesting case that illustrates several important points. This case would likely have been handled very similarly at our institution. The patient is an otherwise young and healthy individual who we would have also considered for upfront autologous SCT consolidation.

You mentioned that the patient was treated with pralatrexate after his relapse, in an effort to reduce his disease prior to SCT. In the original PROPEL (Pralatrexate in Patients With Relapsed or Refractory Peripheral T-cell Lymphoma) study, which evaluated pralatrexate in the treatment of PTCL, there were 6 patients whose data were censored after receiving pralatrexate, 4 of whom responded to pralatrexate by central review of response. These patients went on to receive an SCT (autologous SCT, n=2; allogeneic SCT, n=4).[3] Thus, pralatrexate has been previously successfully used to treat patients who were then able to undergo SCT. Unfortunately, before this patient could undergo SCT, the CSF finding was made.

There are 2 prognostic indices used in PTCL patients: the International Prognostic Index (IPI) and the Prognostic Index for PTCL-NOS (PIT).[4,5] Did you find either of these indices useful when trying to determine if this patient should undergo upfront autologous SCT?

Carlos M. Franco, MD Not in this particular case. Instead, we sent this patient for upfront autologous SCT primarily based on data in ALCL studies showing that ALK-negative patients have a poor prognosis compared with ALK-positive patients.[6]

Leslie L. Popplewell, MD Most of our patients do go on to receive autologous transplant in their first remission.

Carlos M. Franco, MD Yes, in our practice, we generally recommend SCT to most PTCL patients who have achieved remission, regardless of the chemotherapy used. This is especially true for those PTCL patients who are younger and healthier. Most patients do undergo SCT in their first remission.

Leslie L. Popplewell, MD Guidelines from the National Comprehensive Cancer Network (NCCN) recommend that SCT be strongly considered in these patients, especially those with multiple risk factors.[7]

Carlos M. Franco, MD Aside from an elevated LDH, this patient did not have any of the factors typically associated with increased risk (such as anemia, low levels of serum albumin, or weight loss). However, based on his ALK-negative status, combined with a high LDH and his relatively young age, we decided to proceed with upfront autologous SCT. Unfortunately, it proved not to be effective in this case.

Case 2

The second case was a 24-year-old Mexican man with no prior history of any disease. Three weeks before he presented to my clinic, he had visited an emergency department, complaining of abdominal pain. He was found to have a slight fever and was diagnosed with a gastrointestinal infection, for which he was prescribed metronidazole. The patient's condition worsened, and he continued to have fevers. At one point, he had no bowel movements for 3–4 days. This caused him to present to the emergency department again, where he was found to have a 103°F fever. Except for mild leukocytosis, his blood work was essentially unrevealing. However, an x-ray revealed a small bowel obstruction, and a mass was also found in the right neck. During surgery, a tumor was found in the small bowel; the tumor was resected and anastomosis was performed. A pathology review found lymphoma cells in the resected section of the small bowel, at which point I was called.

Upon examination, I confirmed that he had a mass in the right upper neck that essentially extended over the right mandible, measuring approximately 8 cm. There was no other evidence of disease. A bone marrow biopsy was negative, but a PET scan revealed extensive disease. The patient had disease throughout the lymph nodes, several lesions in the liver, and generalized bone disease. The lymphoma was diagnosed as PTCL-NOS; interestingly, there was evidence of a high amount of Epstein-Barr virus (EBV) in the cancer cells.

After I met with the patient and his family, it was decided that he would undergo aggressive upfront therapy; the patient was in the hospital at this time. Just before chemotherapy was initiated, the patient's hemoglobin dropped to 6.5% (from approximately 12% at admission) and he had some blood in his stool. A bleeding scan revealed he had a leak in his anastomosis; however, the surgeon could not find any active bleeding, so he just added more staples around the anastomosis. Unfortunately, after surgery the patient kept bleeding. A disseminated intravascular coagulation (DIC) profile showed he was either in DIC or had a liver coagulopathy with a low fibrinogen

(120 mg/dL). Both prothrombin time and partial thromboplastin time were high, and the patient's platelet count decreased to 30,000 cells/mL. No infections were found at admission, but due to the leak in the anastomosis, the abdominal pain, and the recent surgery, he was prescribed antibiotics (metronidazole and a cephalosporin). The patient continued to have a fever. He was given fresh frozen plasma. We decided to start him on CHOP because he was too sick for hyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone). He remained in the hospital with persistent fevers with negative cultures. He required growth factors, antibiotics, and transfusions. He died with multiorgan failure after the second cycle of chemotherapy.

Discussion

Carlos M. Franco, MD One of the main questions I have regarding this patient involves the presence of EBV in his cancer, and the role that this virus played in his overall clinical picture. The presence of EBV is especially perplexing, given that the patient had never had infectious mononucleosis, any other related infections, or immunosuppression or immune disease

Leslie L. Popplewell, MD This case is interesting because it provides an example of a very acute PTCL presentation. Did the patient have an EBV titer?

Carlos M. Franco, MD Yes. Polymerase chain reaction indicated that he had more than 150,000 copies of the virus, which is consistent with an acute infection. Very interesting.

Leslie L. Popplewell, MD There have been previous reports of EBV-associated PTCL that also had a co-occurring hemophagocytic syndrome[8]; however, it does not sound like this is what was going on with this patient.

Carlos M. Franco, MD No, in fact I personally examined the bone marrow biopsy to see if there was hemophagocytosis, but found no evidence of this.

Leslie L. Popplewell, MD There is no specific treatment for this patient's EBV infection, but there is little else to do except treat the underlying lymphoma.

Carlos M. Franco, MD I agree. The chemotherapy was initially held off due to the patient's bleeding and his need to go back into surgery. However, I spoke with his family members, and I recommended that chemotherapy be initiated anyway. What is your first choice for upfront induction therapy of PTCL?

Leslie L. Popplewell, MD There are a number of combinations recommended by the NCCN guidelines, many of which we use in our practice.[7] However, there are no randomized comparative studies to suggest that other chemotherapy regimens are superior to CHOP. Unfortunately, we still often use CHOP as upfront induction chemotherapy, though remission rates are disappointing and relapse rates are high.

Carlos M. Franco, MD It is essentially the same in our practice. Although our practice is heavily involved in research and we are constantly updating our treatment programs, PTCL is just one of those diseases for which it seems one single treatment is not applicable to all. I just do not think CHOP is good enough for these patients.

Leslie L. Popplewell, MD Yes, and the choice of treatment is complicated by the lack of prospective randomized trials in PTCL patients. Most of the studies that are published have very small patient populations; even if they have larger patient numbers, it is difficult to translate the study to many of the patients seen in the clinic.

Carlos M. Franco, MD I am left to wonder if a weekly multidrug combination would be better, but as you said, there are no studies to support this approach.

Acknowledgment

Dr. Franco has no real or apparent conflicts of interest to report. Dr. Popplewell is a consultant for and has received honoraria and research funding from Allos Therapeutics.

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Case Presentations

Leslie L. Popplewell, MD

Case 1

The patient was a 57-year-old woman with diabetes, hypertension, and a history of PTCL. She presented for diagnosis of skin lesions involving the leg. A biopsy indicated a monomorphic, medium-sized, CD4-positive T-cell lymphoma of the leg. The flow cytometry of the marrow was concerning for possible minimal involvement. The PET/CT scan showed abnormal 18F-fluorodeoxyglucose activity over the right leg only.

The patient was treated with CHOP for 6 cycles. She had some clinical response, with improvement of the leg wound. A follow-up PET scan showed decreased uptake in the right leg, although the uptake did not resolve completely. However, the overlying skin healed nicely. Two months later, the patient developed bleeding from a deep ulcer that opened in the same location as the original lesion. A second biopsy confirmed the recurrence of her lymphoma. She had ongoing significant edema of the leg and required dressing changes of the leg wound due to continual weeping.

At the time of her initial evaluation, her right lower extremity had a purple discoloration over most of the lower leg, with an open ulcerated area on the posterior lower leg that was weeping clear fluid. There were several adjacent open areas. The patient had this covered with a clean, dry dressing with gauze pads over the open areas, all held in place by an elastic bandage. Ambulation was difficult and painful, and she arrived to the office visit in a wheelchair.

The patient was enrolled in the PROPEL trial[1] and began treatment with pralatrexate. By week 3 of cycle 1, clinical improvement was seen, with less edema of the right leg. By the end of cycle 1, there were no areas of tissue breakdown over the right leg, and the area was dramatically improved, although still mildly erythematous.

By the end of cycle 2, the skin lesions were hyperpigmented, but no longer purple or bright red. The skin overlying the lesion was intact, and the skin over the whole leg was loose rather than taut as had previously been the case. The patient completed a third cycle of pralatrexate. At the end of cycle 3, she developed a new PET-positive area over the great toe on the same leg, although not of the original larger lower leg lesion. According to the PROPEL trial criteria, her case was declared a disease progression and she was removed from the study.

Discussion

Carlos M. Franco, MD Was the patient's toe resected or biopsied?

Leslie Popplewell, MD The toe was not resected or biopsied, as the appearance was quite consistent with the appearance of her original disease. This case illustrates the limitations of evaluation by skin photography. The patient never met the criteria established by the PROPEL study for 50% response (a PR), but the improvement in the skin lesions—which are often a manifestation of PTCL—were significant.

Carlos M. Franco, MD One of the things I find most interesting about pralatrexate is that approximately two-thirds of the patients respond during the first 6-week treatment cycle, as shown in the 2009 PROPEL trial.[1] Updated results from the PROPEL trial show that patients have a median duration of response of 10.1 months (Figure 5).[2] In my experience, remissions can be short-lived, which occurred in the first patient case I presented, when the patient developed CNS disease. However, pralatrexate may be superior to another chemotherapy regimen such as ICE, especially when a fast remission is needed prior to an SCT.

Leslie L. Popplewell, MD Yes, in the PROPEL study, the average time to response to pralatrexate was approximately 45 days, very similar to the completion of the first 6-week (42-day) cycle.[1] Some patients may take longer, but overall, if a patient is going to respond to pralatrexate, he or she will do so quickly.

Case 2

This second case was a 75-year-old man with a recent diagnosis of PTCL. Although older, he was active, still worked, and had been a martial arts student for the past 3 decades. His medical history was significant only for some chronic lower back pain, slight arthritis, and a history of carpal tunnel syndrome. He had previously been on atorvastatin to treat hyperlipidemia, and he wore a hearing aid. His family history was unrevealing.

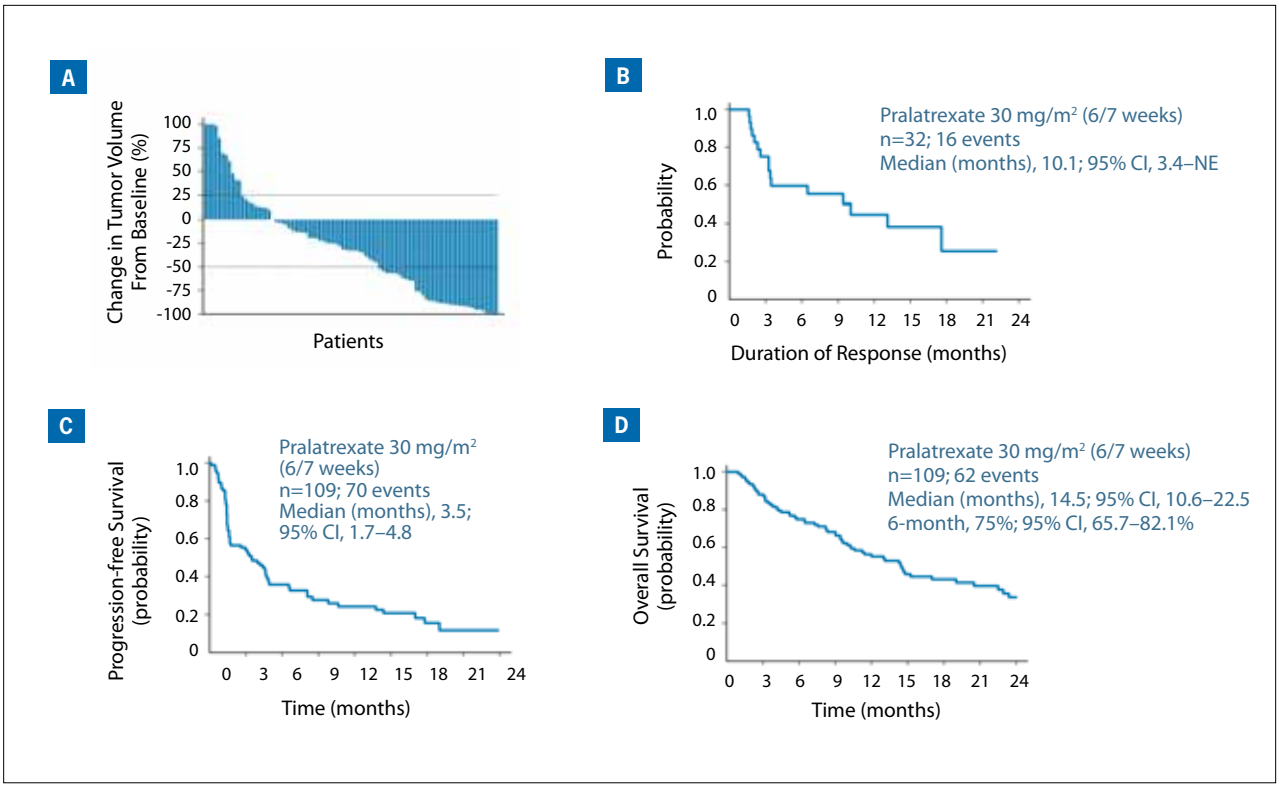

Figure 5. Results from the PROPEL trial. (A) Maximum change from baseline in tumor volume (sum of the products of the greatest diameter). (B) Kaplan-Meier estimate of duration of response per central review. (C) Kaplan-Meier estimate of progression-free survival per central review. (D) Kaplan-Meier estimate of overall survival per central review.

CI=confidence interval; NE=not estimable; PROPEL=Pralatrexate in Patients With Relapsed or Refractory Peripheral T-cell Lymphoma.

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This patient actually noticed his own groin lymphadenopathy when he was exercising. After bringing the swelling to the attention of his physician, a biopsy was performed with the resulting diagnosis of angioimmunoblastic T-cell lymphoma. The patient was referred to an oncologist.

A subsequent bone marrow biopsy was performed, and a pathologic review found it to be positive for lymphoma. A PET/CT scan was performed to stage the patient. These imaging studies revealed involvement in numerous lymph nodes in the cervical, thoracic, abdominal, pelvic, and inguinal areas. The lymphadenopathy was not bulky but was fairly intense by PET scan. The oncologist initiated CHOP therapy.

By the time the patient presented in my office to discuss SCT, he had already received 3 cycles of CHOP. Although he had not undergone a restaging scan since the initiation of therapy, he appeared clinically much improved, particularly showing significant improvement in the palpable adenopathy. The patient was tolerating CHOP very well. Our discussion centered around the prognosis of his particular lymphoma without administration of aggressive therapy, as well as the risk associated with aggressive therapy in patients of his age. As of yet, no other further therapy has been administered.

Discussion

Carlos M. Franco, MD What was the original treatment plan of his primary oncologist?

Leslie L. Popplewell, MD The plan was to give the patient 6 cycles of CHOP chemotherapy. One of the major questions when treating older patients who are responding to treatment is whether or not to intensify the original chemotherapy. However, it is important to remember that when considering age, the patient's physiologic age should be

considered instead of his or her chronologic age. In terms of this particular patient, we decided to continue to administer CHOP, since he was responding well to it and also tolerating it well. Although he had some risk factors (advanced age and bone marrow involvement), he had a good performance status at presentation.

Carlos M. Franco, MD I do not even use the patient's age when considering SCT; the presence of comorbidities is more important. The criteria in our practice is to perform SCTs up to age 78, based on the fact that Medicare approves SCT up to this age for indicated patients.

Overall, autologous SCT is a safe procedure, associated with low morbidity and mortality. In a case such as this patient, an autologous SCT probably does not carry any more significant risk of morbidity or mortality than CHOP itself. SCT is a good option if the patient benefits from induction chemotherapy and achieves a good remission, especially with PTCL, which carries a high risk of recurrence and low long-term survival rate.

Leslie L. Popplewell, MD When discussing treatment options with this patient and his referring oncologist, his prognosis did come up. Using the PIT score,[3] this patient has 2 risk factors, resulting in a predicted 5-year overall survival of 33%. This is quite low. Published reports of upfront transplantation for PTCL are encouraging, and randomized studies are under way. A 2009 study by Reimer and colleagues demonstrated a 3-year disease-free survival of 53%.[4]

After discussing these issues, it was decided that after the patient achieves the best remission he is able to with CHOP, we will reassess and restage him, determining his organ function and disease status. If possible, the patient will undergo SCT at that point.

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Conclusions

Leslie L. Popplewell, MD PTCL is a rare malignancy, resulting in little clinical data. This makes treatment of PTCL patients challenging, and physicians have few large comparative studies to rely on. The introduction of novel agents, either in development or newly approved, has generated much interest in the field regarding these rare lymphomas. Even so, the number of patients available for studies is so low that it has been difficult to provide meaningful answers to questions regarding optimal treatment.

Carlos M. Franco, MD I completely agree. PTCL is a particularly frustrating disease to treat because when we discuss treatment options with patients, there are just not enough data available to feel like an educated decision can be made. Furthermore, the available treatment options are not good enough yet, and patients have high recurrence and mortality rates. Newer agents such as pralatrexate have really only been studied in the relapsed/refractory setting. Upfront therapy of PTCL needs more research, to find the optimal induction regimens to ensure that patients achieve the best response and have the highest hope for survival.

Acknowledgment
Dr. Franco has no real or apparent conflicts of interest to report. Dr. Popplewell is a consultant for and has received honoraria and research funding from Allos Therapeutics.

Commentary

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The term *PTCL* describes a group of lymphomas that arise from a mature (post-thymic) T cell as opposed to an immature (prethymic) T cell. There are many subtypes of PTCL. The cases described in this monograph involve PTCL-NOS, PTCL with skin manifestations (not to be confused with cutaneous T-cell lymphoma [CTCL]), and angioimmunoblastic lymphoma. The discussion raises a number of interesting issues, both in terms of the difficulties in management and the complexities in distinguishing subtypes.

PTCL-NOS and angioimmunoblastic lymphoma are the most common subtypes of PTCL in the United States. The third most common subtype of PTCL is ALCL. All forms of ALCL are characterized histologically by large CD30-positive cells, but clinically they can be subdivided into 3 different clinicopathologic entities. Primary cutaneous ALCL is confined to the skin in most patients and in general follows a chronic relapsing course typical of other indolent non-Hodgkin lymphomas. The 2 systemic forms of ALCL can be distinguished from one another by the expression of the protein ALK-1: ALK-positive ALCL and ALK-negative ALCL. As alluded to in the discussion, the prognosis of these 2 aggressive lymphomas varies. ALK-positive ALCL tends to occur in younger patients and carries a better prognosis. With standard combination chemotherapy such as CHOP, between 60–80% of these patients will be cured. In a recent subset analysis of a series of German prospective studies, these patients had a cure rate above 80% when etoposide was added to CHOP in younger patients.[1] This is one of the rare good-prognosis subtypes of PTCL. ALK-negative anaplastic large-cell lymphoma is a systemic lymphoma that appears the same histologically as the ALK-positive subtype; the only reliable difference is that the cells in ALK-negative anaplastic large-cell lymphoma do not express the ALK protein. ALK-negative anaplastic large-cell lymphoma patients, in general, have a worse prognosis than their ALK-positive counterparts. Their prognosis is more akin to PTCL-NOS, with 15–40% of patients achieving long-term remission depending on risk factors and therapy. To make matters more confusing, the systemic forms of ALCL may also have skin involvement, and primary cutaneous ALCL can occasionally disseminate to lymph nodes. Moreover, the good-prognosis, indolent primary cutaneous ALCL does not express the ALK protein, and it requires clinical correlation to distinguish it from systemic ALK-ALCL. One of the cases highlights this frequently confusing issue. While ALK positivity or negativity is an important prognostic factor in systemic ALCL, its expression is generally not seen and has no known bearing on prognosis or treatment of other types of PTCL, such as PTCL-NOS or angioimmunoblastic T-cell lymphoma.

In Dr. Franco's second case, PTCL presented in the bowel of a man from Mexico. Here again the subclassification of the T-cell lymphomas can be quite confusing. Certainly PTCL-NOS often presents with extranodal disease; however, 2 subtypes of PTCL characteristically present with bowel involvement, often bowel only. They include enteropathy-associated T-cell lymphoma, which develops in patients with celiac disease—sometimes as the initial presentation of that illness—and a subtype of natural killer (NK)/T-cell lymphoma. This latter subtype is more common in Asians, in whom it usually presents in the nasopharynx, but it can present at extranasal sites and frequently occurs in the bowel in patients from Latin America. These aggressive, NK/T-cell lymphomas are usually EBV-driven—as was described in this case—and carry a very poor prognosis. There can be significant overlap in the markers of these lymphomas, and clinical correlation may be needed to most precisely define the subtype. As in the case described by Dr. Franco, these patients are often acutely ill with poor performance status and consequently have a poor tolerance for chemotherapy. There is no clearly preferred strategy for these patients with disseminated NK/T-cell lymphoma (radiation is very important for disease localized to the nasopharynx), and they are usually approached like patients with other aggressive forms of PTCL. Recent studies suggest that L-asparaginase may be active in the nasal NK/T-cell lymphomas, and strategies incorporating this drug into novel regimens are in development.[2]

The features of angioimmunoblastic T-cell lymphoma often overlap with those of other kinds of mature T-cell lymphoma, but there are some specific histologic and immunohistochemical characteristics. Biopsies from these patients often show a mixed cellular infiltrate instead of diffuse or predominant T cells. Large EBV-positive B cells are commonly seen. The malignant T cells usually express CD10 and CXCL13, which can help distinguish this subtype.

Management Approaches

As Dr. Popplewell and Dr. Franco discussed, the standard management for these patients is generally CHOP or CHOP-like regimens. There are many concerns with this approach, however, because most patients will either not

have a complete response or will relapse (or both). However, as Dr. Popplewell correctly points out, many alternative strategies have been investigated, but none are clearly superior to CHOP alone.

A prospective study from Reimer and colleagues looked at upfront autologous transplantation as consolidation of first remission in PTCL.[3] It is one of few prospective studies that provide information about response rates with CHOP alone. Among 83 patients with untreated T-cell lymphomas, the overall response rate to CHOP was approximately 80%, with half being complete responses. However, the durability of the responses is often brief. As Dr. Franco mentioned, there have been a number of attempts to intensify therapy, by increasing the dose intensity or dose density of the chemotherapy. ProMACE-CytaBOM is one such approach. At M.D. Anderson Cancer Center, Pozadzides and coworkers examined their experience with hyper-CVAD,[4] which is a much more dose-intense regimen compared to CHOP, consisting of hyperfractionated cyclophosphamide, with the addition of methotrexate and cytarabine. There appeared to be a higher response rate with hyper-CVAD compared to nonrandomized patients treated with CHOP, but the PFS and the duration of response were not improved. While this study is retrospective, it reinforces the idea that it may not be easy to significantly increase the efficacy of CHOP by adding additional chemotherapy drugs.

The German High-Grade Non-Hodgkin Lymphoma Study Group has performed prospective studies adding etoposide for aggressive lymphomas, including 4-arm studies of CHOP-14, CHOP-21, and CHOP plus etoposide (CHOEP) on the same schedules.[1] These studies enrolled a large number of patients with aggressive lymphoma, primarily DLBCL. The overall conclusion was that, for older patients, CHOP-14 was better than CHOP-21, and for younger patients, the addition of etoposide seemed superior.

Recently this group published their results regarding the subset of patients on these studies with T-cell lymphoma. Interestingly, the majority of the patients in that study had anaplastic large-cell lymphoma; PTCL-NOS and angioimmunoblastic T-cell lymphoma were less common than in other large series. The analysis showed a possible benefit with the addition of etoposide to CHOP for the younger patients with aggressive T-cell lymphomas. However, further subset analysis showed that the majority of the benefit was confined to the good-prognosis patients. The younger patients with ALK-positive ALCL did better when they had etoposide added to standard doses of CHOP as opposed to standard CHOP alone. When these good-prognosis ALK-positive patients were removed from the analysis, the addition of etoposide was associated with a trend toward better event-free survival, but statistical significance was lost.

This subset analysis of a prospective study confirms the results of similar studies. Although CHOP is inadequate, the addition of drugs to make it more dose-dense or dose-intense to date has so far provided only modest or no additional benefit.

Alemtuzumab and denileukin diftitox have also been studied as additions to CHOP. There have been 3 trials in which alemtuzumab was added to CHOP in patients with PTCL. Although the studies were too small and the follow-up was too short to allow definitive conclusions, the preliminary interpretation is that the response rates and the durations of response were not substantially improved with the addition of alemtuzumab. Moreover, alemtuzumab was associated with significant toxicity, including some fatal infections and the development of EBV-positive B-cell lymphomas.[5-7]

A study by Foss and associates examined the addition of denileukin diftitox to CHOP in a phase II study.[8] Denileukin diftitox was given on days 1 and 2, and CHOP was given on day 3. The addition of denileukin diftitox was associated with a higher complete response rate than would be expected with CHOP alone, but there was also significant toxicity. Unexpectedly, several patients died of cardiac arrest in cycle 1.[9]

As both Dr. Franco and Dr. Popplewell mentioned, there is a bias, which I share, in using upfront stem cell transplantation—usually autologous transplants—as consolidation for patients in first remission. This approach is generally used in younger patients who have a complete response. Dr. Popplewell pointed out that in patients in first remission, overall survival at 3 years may be as high as 70%. Upfront transplants are a reasonable approach with a reasonable outcome, although randomized studies testing this hypothesis have not been completed, and patient selection must be weighed when interpreting single-arm studies.

In the large study of upfront autologous stem cell transplant by Reimer and colleagues, the patients—particularly those who received a transplant—did quite well.[3] There was a continuous rate of relapse, however, which extended through the median follow-up of just less than 3 years. This finding raises a question about the use or goals of autotransplant in first remission: Are we really curing more patients or are we perhaps merely delaying relapse? As Dr. Franco pointed out, there are similar debates in mantle cell lymphoma. In T-cell lymphoma, I would argue, both of those results are positive outcomes for the patient, but the expectations when using therapy to achieve a cure as opposed to delay a relapse are quite significant, and these questions may be answered only by randomized studies.

Second-Line Therapies

Drs. Franco and Popplewell also discussed the use of second-line therapies. In 2 of these cases, patients received pralatrexate, with 1 patient participating in the PROPEL

study.[10] We now have a number of interesting and promising new agents for PTCL. The newer agents have been primarily studied in the relapsed setting to try to define their single-agent activity. Pralatrexate is the novel agent with the most published data to date. Pralatrexate is an antifolate but likely has some mechanisms of action that differ from those of methotrexate. It was approved in 2009 for relapsed/refractory T-cell lymphoma on the basis of the PROPEL study, which included 109 evaluable patients—a large number of patients for a phase II study in T-cell lymphoma.[10] The overall response rate in the study was 39% by investigator assessment and 27% by independent central review, and the median duration of response was just over 10 months.

In Dr. Franco's first case, the patient had a remission sufficient to allow transplant. The main side effect of pralatrexate, as seen in this case, is mucositis—particularly oral mucositis or stomatitis. It appears that supplementation with folic acid and vitamin B_{12} may ameliorate some of the worst cases of mucositis, and concurrent administration is a standard supportive measure with this drug.[11] Even with this supplementation, however, mucositis is still the most frequent side effect. It is important to note that in the PROPEL study, although the approved dose was 30 mg/m^2 given intravenously every week for 6 of 7 weeks, on average, patients received between 4 and 5 doses per cycle. Therefore, in many patients, doses were held or skipped, usually due to mucositis or, less often, thrombocytopenia. Importantly, when doses were held for toxicity, response did not appear to be adversely affected. This scenario is common in patients who are treated off-protocol. Often these patients receive a lower dose, for example, 20 mg/m^2 as opposed to 30 mg/m^2, and they receive fewer than 6 weeks of continuous therapy. My colleagues and I have examined the use of pralatrexate at lower doses in cutaneous T-cell lymphoma.[12] We found that in the more indolent forms of cutaneous T-cell lymphoma, an optimal dose of 15 mg/m^2 given 3 of 4 weeks resulted in responses in more than 40% of patients, with what appears to be significantly less toxicity than in the PTCL studies. As we learn more about pralatrexate in the relapsed/refractory setting, we are finding that there is probably a range of ways to dose and schedule this drug; it may not be necessary or optimal for all patients to receive the full approved dose.

Another drug with significant data in PTCL is romidepsin, which is a histone deacetylase inhibitor. It was approved in 2009 for cutaneous T-cell lymphoma. The approved dosage of romidepsin is 14 mg/m^2, given as a 4-hour IV infusion, 3 weeks in a row with 1 week off. This dosing schedule was examined in 130 PTCL patients in a multicenter, registrational trial[13] that was a follow-on to a study from the National Cancer Institute that showed reasonably good results in a variety of patients with relapsed or refractory PTCLs.[14] The registrational romidepsin study showed a 26% response rate, which was similar to that seen with pralatrexate in the PROPEL study. The median duration of response was 12 months, and the median duration for the complete responders had not been reached at the time the data were reported. The main dose-limiting side effect of romidepsin is thrombocytopenia. The more common side effects include mild nausea, fatigue, and malaise. As with pralatrexate, there is a significant minority of patients who have a good response to romidepsin, and in many of these patients, the response can be maintained for a reasonable amount of time to keep their disease under control.

There have been smaller studies looking at other new drugs in PTCL. Lenalidomide showed a 30% response rate in a small Canadian study (N=24) that included patients with relapsed or refractory disease as well as untreated patients.[15] The trial's small size and unusual patient population make it difficult to compare to the other agents; nonetheless, it appears that lenalidomide has activity in PTCL. Gemcitabine and bortezomib are believed to have efficacy and are used in T-cell lymphoma, although larger studies are lacking.

Another new drug on the horizon is SGN-35 (brentuximab vedotin). It is an antibody drug conjugate linking an antitubulin agent to a CD30 antibody. The CD30 antibody delivers the drug to lymphomas that express CD30. In a phase II study of more than 50 systemic anaplastic large-cell lymphoma patients, SGN-35 showed an 86% response rate, with more than 50% of patients having complete responses.[16] There is interest in studying SGN-35 in other T-cell lymphomas that have lower levels and less uniform expression of CD30.

Acknowledgment

Dr. Horwitz has received consulting fees from Allos Therapeutics, Celgene, Seattle Genetics, Millennium, and Novartis. He has performed contracted research for Allos Therapeutics, Celgene, and Genzyme. He has received other honoraria from Merck.

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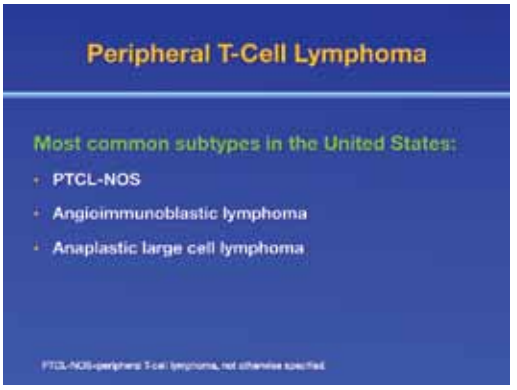

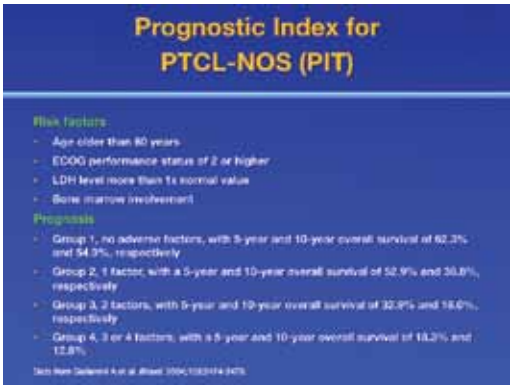

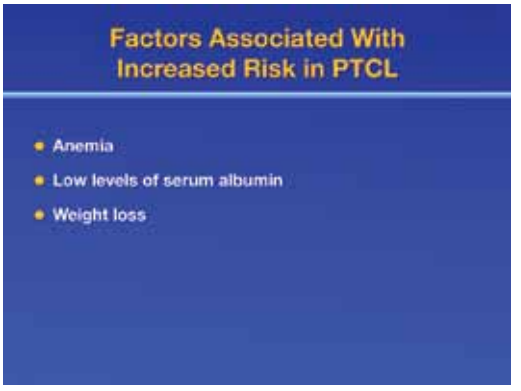

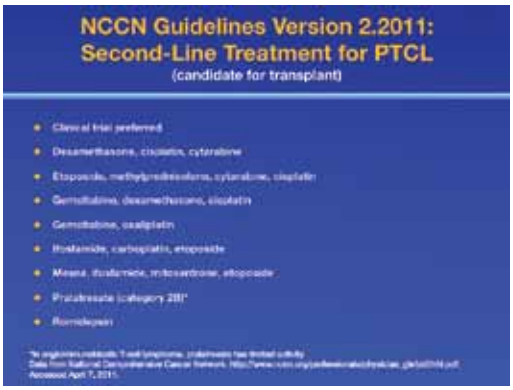

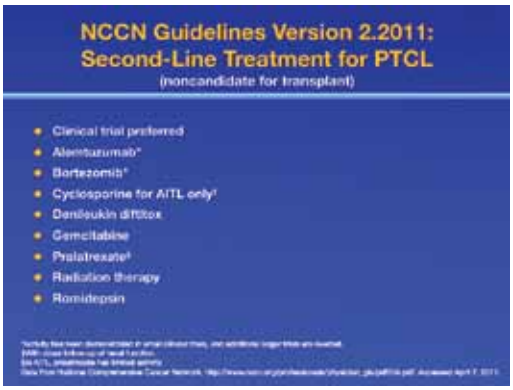

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