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Management of patients with peripheral T-cell lymphoma

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The development of optimal therapy for any disease requires the ability to identify distinct clinical pathological entities likely to respond similarly to a particular treatment. For many years after the development of the first effective treatments for lymphoma, peripheral T-cell lymphomas continued to be lumped with the aggressive B-cell lymphomas in clinical trials. Since these are very different disorders, it is not surprising that the treatments found effective for the more frequent patients with aggressive B-cell lymphoma were not similarly effective for patients with peripheral T-cell lymphoma. The development of the World Health Organization Classification[1] represented an important advance in our ability to care for patients with lymphomas. (Table 1) The major innovation of this new approach was to focus on *real* diseases rather than simply histopathological appearance. The WHO Classification recognized peripheral (i.e. as opposed to central, blastic or thymic) T-cell lymphomas separately and attempted to divide them into distinctive clinical pathological entities.

Expert hematopathologists are able to recognize peripheral T-cell lymphomas in a reproducible manner 85% of the time when immunophenotying is utilized.[2] However, the ability to subdivide the peripheral T-cell lymphomas into specific entities has been more difficult. Some disorders such as ALK-positive anaplastic large cell lymphoma and adult T-cell lymphoma/leukemia can be reproducibly diagnosed more than 90% of the time. However, others such as cutaneous anaplastic large cell lymphoma and hepatosplenic T-cell lymphoma are able to be reproducibly diagnosed only approximately 70% of the time.[3]

To date patients with the various subtypes of peripheral T-cell lymphoma have generally been managed similarly, usually utilizing regimens developed primarily for the treatment of diffuse large B-cell lymphoma. However, it is becoming increasingly apparent that the same approach is not likely to benefit all types of peripheral T-cell lymphoma equally. The various subtypes of peripheral T-cell lymphoma and the results of current management approaches are detailed below.

Peripheral T-cell lymphoma unspecified

In a recent, large international trial peripheral T-cell lymphoma unspecified represented approximately one-quarter of all T-cell lymphomas.[3] This group of illnesses is almost certainly not uniform and might be compared to diffuse large B-cell lymphoma where recently genetic studies demonstrated multiple entities in what was once thought to be an homogenous disorder. In North America most patients with this lymphoma are treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (i.e. CHOP) with disappointing results. The long-term survival for patients with advanced stage peripheral T-cell lymphoma unspecified is on the order of 20% when treated with this or other standard regimens.[4] A number of other agents have been shown to be active in peripheral T-cell lymphoma unspecified. These include nucleoside analogues such as pentostatin, fludarabine, and cladribine.[5] The newer agent gemcitabine, which is the standard therapy for pancreatic cancer, has proven to be highly active in patients with peripheral T-cell lymphoma.[6,7] This drug is among the most promising new agents being studied and is being incorporated into combination chemotherapy regimens that will be tested as part of frontline therapy. Denileukin diftitox, a fusion protein combining diphtheria toxin and

Table 1. Modified WHO classification of T-cell and NK-cell lymphomas.

Classified
Precursor T/NK-Cell Lymphomas
Precursor T-Cell Lymphoblastic Leukemia/Lymphoma
Blastic NK-Cell Lymphoma *(CD4+/CD56+ Hematodermotropic Neoplasm or Plasmacytoid Dendritic Cell Neoplasm)**
Peripheral T/NK-Cell Lymphomas
Extranodal
Extranodal NK/T-Cell Lymphoma, nasal type
Enteropathy-type T-Cell Lymphoma
Hepatosplenic T-Cell Lymphoma
Subcutaneous Panniculitis-like T-Cell Lymphoma *(alpha-beta only)-(Cutaneous γ–δ T-Cell Lymphoma)*
Cutaneous
Mycosis Fungoides/Sézary Syndrome
Primary Cutaneous Anaplastic Large Cell Lymphoma *(Primary Cutaneous Aggressive Epidermotropic CD8+ T-Cell Lymphoma)* *(Primary Cutaneous CD4+ Small/Medium-sized Pleomorphic T-Cell Lymphoma)*
Nodal
Angioimmunoblastic T-Cell Lymphoma
Primary Systemic Anaplastic Large Cell Lymphoma
Peripheral T-Cell Lymphoma (PTCL-u)
Unclassified

**Provisional entities in italics.*

recominent IL-2 receptor, is active in peripheral T-cell lymphomas of all types and not just cutaneous T-cell lymphoma.[8] Alpha interferon is an active agent and can yield complete responses in some patients failing autotransplant.[9] Histone deacetylace inhibitors have activity in cutaneous T-cell lymphoma and are being tested for other peripheral T-cell lymphomas.[10] The anti-CD52 antibody alemtuzumab has also shown activity in these disorders and is being incorporated into combination chemotherapy regimens specifically focusing on the treatment of patients with peripheral T-cell lymphoma. While studies are ongoing, it seems unlikely that this combination will have the effect of adding rituximab to standard regimens for diffuse large B-cell lymphoma.[11-13] Unfortunately, these new agents, with or without more standard antilymphoma drugs, have not yet been incorported into an *effective standard* regimen for the treatment of patients with peripheral T-cell lymphoma unspecified.

Autologous hematopoietic stem cell transplantation is widely used in the United States as initial consolidation treatment for patients with peripheral T-cell lymphoma. However, definitive proof of benefit is lacking.

Allogeneic hematopoietic stem cell transplantation can cure some refractory patients with peripheral T-cell lymphoma. I have treated such a patient who failed standard regimens and an autologous transplant. However, the high mortality has limited the use of this approach. The recent development of reduced intensity transplants, and their lower early mortality have increased interest in allogeneic transplantation for peripheral T-cell lymphoma. At least one series has reported encouraging results.[14] Some American centers offer allogeneic transplantation in first response to high risk patients with peripheral T-cell lymphoma.

Angioimmunoblastic T-cell Lymphoma

Angioimmunoblastic T-cell lymphoma usually presents with an advanced stage, systemic symptoms, and frequently a variety of immunological abnormalities. It is more common in Northern Europe than in other parts of the world.[3] Anthracycline based combination chemotherapy regimens have activity in this disease and appear to be better than the use of prednisone alone.[15] However, long-term disease-free survival rates are still disappointing. While other new agents seem to have activity in angioimmunoblastic T-cell lymphoma, and autologous bone marrow transplantation can occasionally induce long remission, treatment remains suboptimal. A recent report of the benefit of cyclosporine in these patients is encouraging.[16] Cyclosporine appears to sometimes be able to reduce complete remissions that can be durable when used as a single agent. This is being studied in a national trial in the United States.

Anaplastic large T/Null cell lymphoma

Anaplastic large T/null cell lymphoma seems to have a better outlook with standard chemotherapy regimens that are anthracycline based than do other peripheral T-cell lymphomas. Patients whose tumors overexpress anaplastic lymphoma kinase (ALK) seem to have a particularly good outlook.[17] However, it must be remembered that patients who overexpress ALK are typically younger than patients who are ALK negative, and some of the difference in outcome might be related to prognostic factors other than the presence or absence of ALK.[18] Patients with ALK positive anaplastic large T/null cell lymphoma have a high complete remission rate with anthracycline based combination chemotherapy regimens and a long-term disease-free survival of >50%. The results with ALK negative patients is

somewhat inferior, but still better than most other peripheral T-cell lymphomas.[3] Patients who fail standard therapy can sometimes be cured with autologous hematopoietic stem cell transplantation.

Rare extranodal subtypes of peripheral T-cell lymphoma

The most common extranodal peripheral T-cell lymphoma is the extranodal NK/T-cell lymphoma that frequently presents with involvement of the nose or adjacent tissues. This disorder is not rare in Asia where it is one of the most common peripheral T-cell lymphomas. However, it is unusual in the United States.[19] This disorder is highly associated with Epstein Barr virus.[20,21] Patients with localized disease involving the nose and adjacent tissues can sometimes be cured with radiotherapy alone.[22] However, with only radiotherapy most patients subsequently relapse and die. The use of combination chemotherapy and radiotherapy with or without central nervous system prophylaxis is widely used. Recently there have been suggestions that the initial use of radiotherapy followed by chemotherapy, i.e. a different order from what would be used in B-cell lymphomas, might improve outcome.

Enteropathy type T-cell lymphoma occurs most commonly in patients with untreated celiac disease and is particularly frequent in the British Isles and other parts of northern Europe. These patients often present with advanced disease, poor nutrition, poor performance status, and frequently intestinal perforation. Standard chemotherapy regimens have been largely ineffective with a five-year failure-free survival rate of only 3% in one large series.[23] There is hope that appropriate treatment for celiac disease might prevent this lymphoma.[24] Aggressive treatment approaches have not seemed to improve outcome.[25] Hepatosplenic T-cell lymphoma is a rare entity that usually presents with systemic symptoms, hepatosplenomegaly, and cytopenias. Although case reports have described a good outlcome with penostatin or platinum based treatment regimens,[26,27] the results of treating these patients has been almost uniformly poor.

Subcutaneous panniculitis like T-cell lymphoma is also an extremely rare entity. Some patients have an indolent, recurring cutaneous disease that is managed by a dermatologist, while others can have a systemic disorder that is rapidly fatal. Systemic treatments for progressive disease have been disappointing, but local symptoms can be controlled with radiotherapy.

Conclusions

The peripheral T-cell lymphomas represent a therapeutic challenge that has not yet been met. Patients with these diseases have a much lower chance to survive their lymphoma than patients with similar B-cell lymphomas. Clinical trials focusing on these disorders are desperately needed to identify treatment regimens that will be uniquely beneficial to patients with peripheral T-cell lymphoma. Fortunately, these studies are now beginning to be carried out by clinical research groups throughout the world.

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