clinical review

Practical Treatment Approach for Angioimmunoblastic T-Cell Lymphoma

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abstract

Patients with angioimmunoblastic T-cell lymphoma (AITL), one of the most common types of peripheral T-cell lymphoma (PTCL), typically present with advanced disease, systemic symptoms, and immune deregulation. Treatment can be challenging owing to frequent relapses after initial and subsequent therapy. The front-line treatment approach currently mirrors the approach used for other nodal PTCLs with cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy and consideration for autologous stem-cell transplant (SCT). In the relapsed and refractory settings, allogeneic SCT offers the chance for long-term remission. Choice of treatment of relapsed or refractory disease depends on whether an allogeneic SCT is planned. Agents with preferential activity in relapsed or refractory AITL include epigenetic modifiers such as histone deacetylase inhibitors and hypomethylating agents. Other targeted agents show promise in AITL, including brentuximab vedotin and phosphoinositide-3-kinase inhibitors. Ongoing studies are evaluating new potential targets for AITL, with particular focus on identifying markers of response and resistance. Additional studies are assessing incorporation of novel agents into the front-line treatment of AITL. These studies will lead to more individualized treatment approaches and, ultimately, improved outcomes for patients with AITL.

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CASE PRESENTATION

A 74-year-old previously healthy woman arrived for consultation with a 1-month history of progressive fatigue, dyspnea, orthopnea, anorexia, and night sweats. The examination was significant for enlarged cervical, axillary, and inguinal lymphadenopathy, splenomegaly, a diffuse maculopapular rash, and reduced breath sounds at the lung bases. Laboratory tests revealed thrombocytopenia (62 K/μL), autoimmune hemolytic anemia (hemoglobin, 7.5 g/dL; reticulocyte percentage, 7.5%; haptoglobin level, < 1 mg/dL; positive direct Coombs test), hypoalbuminemia (3.1 g/dL), elevated lactate dehydrogenase (LDH; 327 U/L), and mild hyponatremia (133 mEq/L). Positron emission tomography (PET) scan confirmed the examination findings, showing hypermetabolic lymphadenopathy in the cervical, axillary, retroperitoneal, and pelvic regions; splenomegaly; and moderate bilateral pleural effusions. Findings on examination of an excisional right-side inguinal lymph node biopsy specimen were consistent with angioimmunoblastic T-cell lymphoma (AITL). A bone marrow biopsy specimen was moderately hypercellular (80%) and showed trilineage hematopoiesis with a moderately increased number of megakaryocytes and 5% involvement by AITL.

The patient was administered prednisone 100 mg/d and had marked improvement in her symptoms, stabilization of her blood cell counts, and improvement in her performance status. Chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was subsequently initiated.

CLINICAL AND PATHOLOGIC CHARACTERISTICS OF AITL

AITL is a malignancy derived from mature T-follicular helper (TFH) cells, a subset of T cells normally responsible for supporting B-cell maturation and germinal center development.[1] Historically, AITL was considered a nonmalignant lymphoproliferation and various terms have been used to describe the syndrome observed with AITL, such as angioimmunoblastic lymphadenopathy with dysproteinemia, immunoblastic lymphadenopathy, or lymphogranulomatosis X. More recently, the advent of immunophenotyping and identification of T-cell clonality in the majority of cases led to the recognition of AITL as a de novo malignant process. Since the 1980s, it has been recognized as a distinct entity in lymphoma classifications.[2,3]

AITL is one of the most common subtypes of peripheral T-cell lymphoma (PTCL), representing 18.5% of all T-cell lymphomas; higher prevalence is noted in Europe.[4] Clinically, it is characterized as aggressive; patients typically are seen at first consultation with advanced disease associated with systemic symptoms,

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rash, pleural effusions, polyclonal hypergammaglobulinemia, ascites, and autoimmune phenomenon.

Diagnosis is made by evaluation of a lymph node biopsy specimen, which shows partial or total effacement of the lymph node architecture with small to medium atypical T cells with clear to pale cytoplasm. The atypical cells are typically positive for CD4, CD5, and CD2, as well as markers of TFH cells such as CD10, CXCL13, ICOS, BCL6, and PD1. The neoplastic cells frequently cluster adjacent to high endothelial venules and are surrounded by increased follicular dendritic cell meshworks and polymorphous inflammatory cell infiltrates consisting of reactive lymphocytes, histiocytes, plasma cells, and eosinophils. B immunoblasts are usually present, which are positive for Epstein-Barr virus (EBV) in 80% to 95% of cases and can develop into EBV-positive, diffuse large B-cell lymphoma. Given the extensive inflammatory background observed in lymph nodes in patients with AITL, excisional lymph node biopsies are often required for diagnosis. Work-up consists of routine testing such as CBC count, comprehensive metabolic panel, measurement of LDH concentration, testing for human T-lymphotropic virus-1, HIV, and hepatitis B and C, as well as PET/computed tomography (CT) imaging, and bone marrow biopsy.

Gene expression profiling has identified several recurrent mutations associated with AITL, including genes encoding epigenetic modifiers such as TET2 (80%), DNMT3A (20% to 30%), and IDH2 (20% to 30%), as well as the gene for the GTPase RHOA (50% to 70%).[5] Interestingly, a similar mutation profile is observed in a rare subtype of T-cell lymphoma, called follicular T-cell lymphoma, and approximately 20% to 30% of cases of PTCL not otherwise specified (PTCL-NOS). The recognition of this subset of PTCL-NOS led to the designation of a new provisional entity in the 2016 WHO classification called nodal PTCL with TFH phenotype. In addition to molecular similarities, there is overlap in the pathologic and clinical manifestations of follicular T-cell lymphoma, PTCL with TFH phenotype, and AITL. Therefore, it is possible that these entities may respond to similar therapies; however, studies are needed for confirmation.

FRONT-LINE TREATMENT OF AITL

The choice of front-line treatment depends on the goal of therapy. For most patients with AITL, the initial goal of treatment is curative; therefore, an aggressive approach with combination chemotherapy followed often by consolidation with autologous stem-cell transplant (ASCT) is used. For elderly patients, or those with significant comorbidities, milder therapy (such as corticosteroids with or without low-dose chemotherapy) may be appropriate. Although this approach is not curative, it does provide the potential for prolonged disease control and maintenance of quality of life. Options in this scenario include intermittent courses of single-agent prednisone, combination chemotherapy (such as low-dose cyclophosphamide and etoposide combined with prednisone) or single-agent chemotherapy, such as those listed in Table 1, for relapsed or refractory disease. These treatments can often suppress the symptoms that accompany AITL; typically, however, ongoing therapy is required at some frequency for maintenance of disease control.

For most patients who are candidates for at least combination chemotherapy, AITL is treated similarly to other nodal PTCLs, and CHOP has been the backbone for front-line treatment. The overall response rate (ORR) and complete response (CR) rate with CHOP for patients with all-nodal PTCLs (using CT-based response criteria) are 70% to 79% and 35% to 39%, respectively; however, despite fairly high response rates, long-term outcomes with CHOP alone is generally poor, owing to high relapse rates.[16,17] In the International T-Cell Lymphoma Project, in which 85% of patients received CHOP-based therapy (without upfront ASCT consolidation), the 5-year failure-free survival rate for patients with AITL was only 18%.[4] Similar outcomes were observed in the British Columbia Cancer Agency series, in which the 5-year progression-free survival (PFS) observed for AITL was only 13%.[18] Likewise,

TABLE 1. Active Agents for Relapsed or Refractory AITL

Agents	AITL (No.)	ORR/CR (AITL), %	Total PTCL (No.)	ORR/CR (all PTCL)	PFS (median months)	DOR (median months)
Romidepsin[6]	27	30/19	130	25/15	4	17
Belinostat[7,8]	22	45/18	129	26/10	NA	8.3
5-Azacytidine[9]	12	75/42	19	53/26	NA	NA
Pralatrexate[10]	13	8/NR	111	29/13	3.5	10.5
Bendamustine[11]	32	NR	60	50/28	3.6	3.5
Brentuximab vedotin[12]	13	54/38	22	41/24	2.6	7.6
Gemcitabine[13]	NR	NR	20	55/30	NR	NR
Lenalidomide[14]	7	29/0	23	30/0	3.2	5.7
Cyclosporine A[15]	12	67/25	NA	NA	NA	NA

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; CR, complete response; DOR, duration of response; NA, not applicable; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma.

5-year PFS was only 20% for patients with PTCL in the Swedish Lymphoma Registry who received CHOP-based therapy alone.[19]

Building Upon the CHOP Backbone

Attempts to improve front-line therapy for nodal PTCLs have included adding additional agents to the CHOP backbone and consolidating CHOP-based induction with ASCT. On the basis of limited data in PTCL, CHOP plus etoposide is among the most common regimens used for younger, fit patients. Support for this regimen comes from an analysis from the German high-grade non-Hodgkin lymphoma study group of patients with PTCL treated using seven different prospective phase II or phase III protocols comparing CHOP-based therapy with CHOP plus etoposide-based therapy.[20] Among the 320 patients with PTCL enrolled in these studies, younger patients (< 60 years) with normal LDH values had a significant improvement in outcome if they received CHOP plus etoposide compared with CHOP alone, with 3-year event-free survival of 75.4% versus 51%, although no difference in overall survival (OS) was observed. In elderly patients, there was no benefit from the addition of etoposide, because of toxicity. Improved outcomes with CHOP plus etoposide versus CHOP were also observed in the Swedish Lymphoma Registry, data from which indicated treatment with CHOP plus etoposide in PTCL yielded a higher ORR (81% *v* 70%; $P = .052$) and improved PFS for patients younger than age 60 years treated with CHOP plus etoposide (hazard ratio, 0.49; 95% CI, 0.29 to 0.83; $P = .008$).[9]

Other agents that have been evaluated in combination with CHOP in PTCL include alemtuzumab, romidepsin, bortezomib, and belinostat.[21-24] In general, there is a suggestion of improved CR rates when these agents are added to CHOP; however, increased toxicities are observed as well; therefore, phase III studies are needed to establish the role of these regimens. We await final results from phase III studies evaluating romidepsin plus CHOP and alemtuzumab plus CHOP in PTCL. Additional studies exploring regimens that abandon the CHOP backbone, such as etoposide, ifosfamide, cisplatin alternating with doxorubicin, bleomycin, vinblastine, dacarbazine; cisplatin, etoposide, gemcitabine, and solumedrol; and gemcitabine, etoposide, and cisplatin, have not yet been successful in showing improvements over CHOP.[17,25,26] Perhaps the most likely drug to influence the front-line treatment of at least a subset of patients with AITL is brentuximab vedotin (BV), the anti-CD30 antibody drug conjugate. CD30 positivity is observed in 43% to 90% of cases of AITL and in a phase II study, BV induced objective responses in 54% of patients with CD30-positive relapsed or refractory AITL.[12,27,28] The highly anticipated results from ECHELON-2, a phase III study comparing CHOP with cyclophosphamide, doxorubicin, and prednisone–BV in untreated, CD30-positive T-cell lymphoma will determine whether the cyclophosphamide, doxorubicin, and prednisone–BV regimen will become a new standard for front-line treatment of CD30-positive AITL.

Upfront Consolidation With ASCT

To further improve on the outcomes with CHOP-based therapy, many groups routinely offer consolidation with ASCT in first remission for patients with AITL and other PTCLs. There are no randomized trials to support this treatment approach; however, several results of prospective phase II studies suggest benefit from upfront ASCT, whereas other analyses show conflicting results. The largest prospective study evaluating upfront consolidation with ASCT was the Nordic study by d'Amore et al.[29] This study enrolled 160 patients with PTCL, including 39% with PTCL-NOS and 19% with AITL. Most patients (81%) had advanced stage disease and 72% had international prognostic index scores greater than or equal to 2. Patients received CHOP plus etoposide for six cycles (etoposide was omitted for patients > 60 years of age) and those in CR or PR proceeded to high-dose therapy with carmustine, etoposide, cytarabine, and melphalan (or cyclophosphamide) and ASCT. A total of 115 patients (71%) underwent ASCT. By intent-to-treat analysis, the 5-year OS and PFS were 51% and 44%, respectively, which compare favorably to historical series. For patients with AITL, 5-year OS and PFS were 52% and 49%, respectively. Reimer et al[16] reported similar results in a phase II study of CHOP followed by ASCT for 83 patients with PTCL; the 3-year OS was 48%.

Several retrospective and population-based series evaluating upfront consolidation with ASCT closely mirror the experience in prospective studies. In the Swedish Lymphoma Registry, intent to treat with ASCT in first remission was associated with 5-year OS of 48% compared with 26% ($P = .004$).[9] Similar results were seen in a retrospective series from Memorial Sloan Kettering Cancer Center (MSKCC) and in the Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment database, both of which showed improved outcomes for patients with PTCL undergoing ASCT in first remission.[30-32] In contrast, a multicenter retrospective series from 14 centers in France, Portugal, and Belgium of 269 patients with PTCL (including 46% with AITL) observed no benefit of upfront consolidation with ASCT for patients achieving CR or PR after induction therapy.[33] A major criticism of the analysis was that patients with poor risk factors were disproportionately represented in the ASCT group. To provide balance between the two groups, a propensity score matching analysis was performed, however, this markedly reduced the number of patients analyzed to only 73 per group. Given the inherent bias associated with retrospective analyses and observational studies, the results of all these series need to be interpreted cautiously. In the absence of phase III data, the results from prospective phase II studies provide the strongest evidence in support of upfront consolidation with ASCT. Thus, outside of a clinical trial, induction with CHOP plus etoposide followed by consolidation with ASCT is a

reasonable approach for patients with PTCL, including AITL. However, whenever possible, enrollment in clinical trials should be favored.

CASE PRESENTATION CONTINUED

The 74-year-old woman with stage IV AITL received six cycles of CHOP chemotherapy. PET imaging and evaluation of a bone marrow biopsy specimen at end of treatment confirmed a CR. She underwent stem cell mobilization in preparation for upfront consolidation with ASCT; however, shortly after completion of mobilization (approximately 4 weeks after cycle 6 of CHOP), she reported return of low-grade fevers and increasing fatigue. Laboratory tests showed mild worsening of anemia and new hypoalbuminemia. Repeated PET imaging showed low-volume generalized fluorodeoxyglucose -avid lymphadenopathy and CT-guided inguinal lymph node biopsy confirmed relapsed AITL. She enrolled in a phase I clinical trial evaluating romidepsin, carfilzomib, and lenalidomide, with the plan to consider consolidation with allogeneic SCT (alloSCT).

RELAPSED/REFRACTORY AITL

Owing to the possibility of development of EBV-related diffuse large B-cell lymphoma either concurrently with AITL or at relapse, repeated biopsy is essential to confirm the etiology of relapsed or refractory disease. The approach to treatment of patients with relapsed/refractory AITL (as well as the other nodal PTCLs) depends on the whether the goal of therapy is cure or palliative.[34] There are multiple regimens that can induce disease control and possibly remission in AITL; however, the choice of therapy and how to sequence treatment depends heavily on whether consolidation with an alloSCT is being considered.

What Is the Consolidation Plan: ASCT, alloSCT, or Neither?

Although ASCT is routinely used in the relapsed/refractory setting for B-cell lymphomas, results from several series (Table 2) demonstrated disappointing outcomes when ASCT was used for relapsed/refractory PTCL.[35,36] In particular, data from the Cleveland Clinic and from MSKCC show relapse rates greater than 80% when ASCT is used for relapsed/refractory PTCL.[35,36] In contrast, Center for International Blood and Marrow Transplant Research registry data suggest more promising results with ASCT for relapsed PTCL; however, this series is heavily represented by patients with anaplastic large-cell lymphoma, which may explain the more favorable outcomes observed. Therefore, with the exception of anaplastic large-cell lymphoma, ASCT is unlikely to lead to long-term remission for patients with relapsed/refractory AITL and other PTCLs.[37] More promising outcomes are observed with alloSCT, which is associated with a 2- to 5-year PFS of 45% to 53% for nodal PTCLs and as high as 81% for AITL.[38-41] Therefore, for appropriate patients, consolidation with alloSCT is strongly considered provided disease control can be obtained.

What Should Be Used to Achieve Disease Control in the Relapsed/Refractory Setting?

The choice of initial therapy for relapsed or refractory AITL depends on whether alloSCT is being considered and whether a donor has already been identified. When an alloSCT is planned and a donor is identified, regimens likely to induce response quickly are reasonable. For example, a regimen such as ifosfamide, carboplatin, and etoposide, which is associated with response rates up to 70%, can efficiently bridge patients to transplantation; however, the ifosfamide, carboplatin, and etoposide regimen would not be expected to produce sustained disease control, because of cumulative toxicity after three or four cycles.[35] Therefore, when an alloSCT is either not part of the treatment plan (owing to age, comorbidities, or lack of donor) or the timing of alloSCT is unclear, drugs or regimens capable of producing sustained disease control are appropriate. Such treatments are potentially less likely to cause cumulative toxicity with continuous therapy and include single agents, milder combinations, or novel approaches in clinical trials. As shown in Table 1, which summarizes the response rates for select agents used for AITL, histone deacetylase inhibitors seem to have preferential activity in AITL, likely related to the high frequency of mutations in epigenetic modifier genes seen in this disease. Accordingly, histone deacetylase inhibitors, either alone or in combination with other agents (as part of clinical trials) are typically the first treatment choice for patients with relapsed or refractory AITL.

FUTURE DIRECTIONS FOR TREATMENT OF AITL

Epigenetic Modifiers

Given the signal of activity of histone deacetylase inhibitors in AITL, regimens building on these agents are likely to make a significant impact on treatment. As stated, in the front-line setting, the safety of adding romidepsin to CHOP has been established and this regimen is currently being evaluated in a phase III study comparing romidepsin plus CHOP with CHOP alone.[24] In the relapsed and refractory settings, romidepsin combinations were evaluated in two phase I studies at MSKCC, first in combination with lenalidomide and subsequently in combination with lenalidomide and carfilzomib. The two studies enrolled a total of 19 patients with PTCL, including seven patients with AITL. The ORR and CR rates for the patients with AITL (87% and 57%, respectively) were considerably higher than observed in the other patients with PTCL (ORR, 33%), further supporting the potential role of histone deacetylase inhibitor–based therapy in AITL.[41,42]

Hypomethylating agents are another class of epigenetic modifiers that seem promising for AITL. A recent study evaluating 5-azacytidine in PTCLs (n = 12 patients with

TABLE 2. Outcomes With Autologous Stem-Cell Transplant and Allogeneic Stem-Cell Transplant for Relapsed/Refractory PTCL

			Autologous SCT, % (median follow-up)		Allogeneic SCT, % (median follow-up)	
Series	**PTCL (No.)**	**AITL (No.)**	**OS**	**PFS**	**OS**	**PFS**
MSKCC (auto)[36]	40	5	45 (45 months)	17 (3 years)	NA	NA
Cleveland Clinic (auto)[37]	32	NA	34 (5 years)	RFS, 18 (5 years)	NA	NA
CIBMTR[38]	75* (auto beyond CR 1)	5 (auto beyond CR 1)	53 (3 years)	42 (3 years)	41 (3 years)	31 (3 years)
	108 (allo beyond CR 1)	12† (allo)				
French Registry[39]	77	11	NA	NA	57 (5 years) For AITL: 80 (5 years)	53 (5 years)
MSKCC (allo)[40]	65	11	NA	NA	59 (2 years)	48 (2 years) For AITL: 81 (2 years)
Dana Farber Cancer Institute[41]	52‡	5	NA	NA	41 (3 years) For nodal histologies: 52 (3 years)	30 (3 years) For nodal histologies: 45 (3 years)

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; allo, allogeneic; auto, autologous; CIBMTR, Center for International Blood and Marrow Transplant Research; CR 1, first complete response; MSKCC, Memorial Sloan Kettering Cancer Center; NA, not applicable; OS, overall survival; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma; RFS, relapse-free survival; SCT, stem-cell transplant.

*52% anaplastic large-cell lymphoma; 37% PTCL not otherwise specified; 8% AITL.

†Included 10 patients in CR 1.

‡Number beyond CR 1 not reported.

AITL and n = 7 patients with other PTCLs) reported an ORR of 53%. Preferential activity was observed in AITL, with nine of 12 patients (75%) achieving response and five of 12 (42%) achieving CR.[9] Studies building on this class in PTCL, including AITL, are underway (ClinicalTrials.gov identifiers: NCT03161223 and NCT01998035).

Other Targets: CD30, PI3K, JAK/STAT

As mentioned, a significant portion of AITL cases express CD30, and BV has activity in relapsed and refractory CD30-positive disease.[12] In addition, it is possible that BV will affect the front-line treatment of CD30-positive AITL if results of the ECHELON-2 study are positive. Additional pathways that may prove to be important targets in PTCL, including AITL, are the phosphoinositide-3-kinase (PI3K) and Janus kinase (JAK)/signal transducers and activator of transcription (STAT) pathways. A phase I/II study of the PI3K-δ/γ inhibitor duvelisib in patients with relapsed/refractory PTCL showed promising single-agent activity, with an ORR of 50%, including prolonged responses in AITL.[43] Duvelisib is being evaluated in combination with romidepsin and bortezomib in parallel phase I studies for PTCL and preliminary results included sustained responses in AITL.[44] The identification of JAK/STAT gain-of-function mutations in AITL provides rationale for evaluating JAK inhibitors in this disease.[45] Preliminary results from a phase II study with cerdulatinib, the dual JAK/SYK inhibitor, demonstrate an initial signal of activity in PTCL.[46] The clinical role of JAK inhibition in AITL (and other T-cell lymphomas) is formally being evaluated in a phase II study of ruxolitinib in PTCL (ClinicalTrials.gov identifier: NCT02974647).

In conclusion, although AITL has typically been grouped with the other T-cell lymphomas with regard to management, data are emerging regarding its unique targets and sensitivity to certain agents. These data will eventually lead to the development of regimens specific for AITL as well as potentially for the TFH-like provisional entities follicular T-cell lymphoma and nodal PTCL with TFH phenotype. Even among patients with AITL, there is heterogeneity with regard to molecular profiling and sensitivity to agents. Studies evaluating novel agents in AITL that include assessments of baseline and on-treatment biopsy specimens, aimed at identifying markers of response or resistance, will aid in determining which drugs or regimens are most appropriate for individuals. Eventually, pathologic and molecular profiling may allow for stratification of patients with AITL at diagnosis and treatment according to likelihood of sensitivity to histone deacetylase inhibitors, hypomethylating agents, anti-CD30 treatment, and other targeted agents. A more individualized front-line approach will undoubtedly lead to improved outcomes for patients with AITL.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Swerdlow SH, Campo E, Harris NL, et al (eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised 4th ed). Lyon, France, International Agency for Research on Cancer, 2017.
2. Dogan A, Attygalle AD, Kyriakou C: Angioimmunoblastic T-cell lymphoma. Br J Haematol 121:681-691, 2003
3. de Leval L, Gisselbrecht C, Gaulard P: Advances in the understanding and management of angioimmunoblastic T-cell lymphoma. Br J Haematol 148:673-689, 2010
4. Vose J, Armitage J, Weisenburger D: International peripheral T-cell and natural killer/T-cell lymphoma study: Pathology findings and clinical outcomes. J Clin Oncol 26:4124-4130, 2008
5. Lemonnier F, Gaulard P, de Leval L: New insights in the pathogenesis of T-cell lymphomas. Curr Opin Oncol 30:277-284, 2018
6. Coiffier B, Pro B, Prince HM, et al: Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol 30:631-636, 2012
7. Horwitz S, O'Connor O, Jurczak W, et al: Belinostat in relapsed or refractory peripheral T-cell lymphoma subtype angioimmunoblastic T-cell lymphoma: Results from the pivotal BELIEF trial. Hematol Oncol 31:147, 2013 (suppl. 1)
8. O'Connor OA, Horwitz S, Masszi T, et al: Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: Results of the pivotal phase II BELIEF (CLN-19) Study. J Clin Oncol 33:2492-2499, 2015
9. Delarue R, Dupuis J, Sujobert P, et al: Treatment with hypomethylating agent 5-azacytidine induces sustained response in angioimmunoblastic T cell lymphomas. Blood 128:4164, 2016
10. O'Connor OA, Pro B, Pinter-Brown L, et al: Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: Results from the pivotal PROPEL study. J Clin Oncol 29:1182-1189, 2011
11. Damaj G, Gressin R, Bouabdallah K, et al: Results from a prospective, open-label, phase II trial of bendamustine in refractory or relapsed T-cell lymphomas: The BENTLY trial. J Clin Oncol 31:104-110, 2013
12. Horwitz SM, Advani RH, Bartlett NL, et al: Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. Blood 123:3095-3100, 2014
13. Zinzani PL, Venturini F, Stefoni V, et al: Gemcitabine as single agent in pretreated T-cell lymphoma patients: Evaluation of the long-term outcome. Ann Oncol 21: 860-863, 2010
14. Dueck G, Chua N, Prasad A, et al: Interim report of a phase 2 clinical trial of lenalidomide for T-cell non-Hodgkin lymphoma. Cancer 116:4541-4548, 2010
15. Advani R, Horwitz S, Zelenetz A, et al: Angioimmunoblastic T cell lymphoma: Treatment experience with cyclosporine. Leuk Lymphoma 48:521-525, 2007
16. Reimer P, Rüdiger T, Geissinger E, et al: Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: Results of a prospective multicenter study. J Clin Oncol 27:106-113, 2009
17. Simon A, Peoch M, Casassus P, et al: Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T cell lymphoma. Results of the randomized phase III trial GOELAMS-LTP95. Br J Haematol 151:159-166, 2010
18. Savage KJ, Chhanabhai M, Gascoyne RD, et al: Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol 15:1467-1475, 2004
19. Ellin F, Landström J, Jerkeman M, et al: Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: A study from the Swedish Lymphoma Registry. Blood 124:1570-1577, 2014
20. Schmitz N, Trümper L, Ziepert M, et al: Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 116:3418-3425, 2010
21. Gallamini A, Zaja F, Patti C, et al: Alemtuzumab (Campath-[1]H) and CHOP chemotherapy as first-line treatment of peripheral T-cell lymphoma: Results of a GITIL (Gruppo Italiano Terapie Innovative nei Linfomi) prospective multicenter trial. Blood 110:2316-2323, 2007
22. Kim SJ, Yoon DH, Kang HJ, et al: Bortezomib in combination with CHOP as first-line treatment for patients with stage III/IV peripheral T-cell lymphomas: a multicentre, single-arm, phase 2 trial. Eur J Cancer 48:3223-3231, 2012
23. Johnston PB, Cashen AF, Nikolinakos PG, et al: Safe and effective treatment of patients with peripheral t-cell lymphoma (PTCL) with the novel HDAC inhibitor, belinostat, in combination with CHOP: Results of the Bel-CHOP phase 1 trial. Blood 126:253, 2015
24. Dupuis J, Morschhauser F, Ghesquières H, et al: Combination of romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated patients with peripheral T-cell lymphoma: A non-randomised, phase 1b/2 study. Lancet Haematol 2:e160-e165, 2015
25. Mahadevan D, Unger JM, Persky DO, et al: Phase II trial of cisplatin plus etoposide plus gemcitagine plus solumedrol (PEGS) in peripheral T-cell non-Hodgkin lymphoma (SWOG S0350). Cancer 119: 371-379, 2013
26. Gleeson M, Peckitt C, To YM, et al: CHOP versus GEM-P in previously untreated patients with peripheral T-cell lymphoma (CHEMO-T): A phase 2, multicentre, randomised, open-label trial. Lancet Haematol 5:e190-e200, 2018
27. Onaindia A, Martínez N, Montes-Moreno S, et al: CD30 expression by B and T cells: A frequent finding in angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma-not otherwise specified. Am J Surg Pathol 40:378-385, 2016
28. Sabattini E, Pizzi M, Tabanelli V, et al: CD30 expression in peripheral T-cell lymphomas. Haematologica 98:e81-e82, 2013
29. d'Amore F, Relander T, Lauritzsen GF, et al: Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol 30: 3093-3099, 2012

30. Mehta N, Maragulia JC, Moskowitz A, et al: A retrospective analysis of peripheral T-cell lymphoma treated with the intention to transplant in the first remission. Clin Lymphoma Myeloma Leuk 13:664-670, 2013
31. Mehta-Shah N, Ito K, Bantilan KS, et al: Interim PET evaluation by Deauville criteria is an effective risk stratification tool in PTCL. Blood 128:186, 2016
32. Park SI, Horwitz SM, Foss FM, et al: The role of upfront hematopoietic stem cell transplantation (HSCT) in peripheral T-Cell Lymphoma (PTCL) patients in complete remission (CR) with a special focus on nodal PTCL: Report from the Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE), a Prospective multicenter cohort study. Presented at: 59th ASH Annual Meeting, Atlanta, GA, December 9-12, 2017
33. Fossard G, Broussais F, Coelho I, et al: Role of up-front autologous stem-cell transplantation in peripheral T-cell lymphoma for patients in response after induction: An analysis of patients from LYSA centers. Ann Oncol 29:715-723, 2018
34. Lunning MA, Moskowitz AJ, Horwitz S: Strategies for relapsed peripheral T-cell lymphoma: The tail that wags the curve. J Clin Oncol 31:1922-1927, 2013
35. Horwitz S, Moskowitz C, Kewalramani T, et al: Second-line therapy with ICE followed by high dose therapy and autologous stem cell transplantation for relapsed/refractory peripheral T-cell lymphomas: Minimal benefit when analyzed by intent to treat. Blood 106: 2679, 2005
36. Smith SD, Bolwell BJ, Rybicki LA, et al: Autologous hematopoietic stem cell transplantation in peripheral T-cell lymphoma using a uniform high-dose regimen. Bone Marrow Transplant 40:239-243, 2007
37. Smith SM, Burns LJ, van Besien K, et al: Hematopoietic cell transplantation for systemic mature T-cell non-Hodgkin lymphoma. J Clin Oncol 31:3100-3109, 2013
38. Le Gouill S, Milpied N, Buzyn A, et al: Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: A study by the Société Francaise de Greffe de Moëlle et de Thérapie Cellulaire. J Clin Oncol 26:2264-2271, 2008
39. Mehta-Shah N, Chou J, Maloy M, et al: Successful treatment of peripheral T-Cell lymphoma with allogeneic stem cell transplantation: A large single-center experience. Blood 126:4392, 2015.
40. Jacobsen ED, Kim HT, Ho VT, et al: A large single-center experience with allogeneic stem-cell transplantation for peripheral T-cell non-Hodgkin lymphoma and advanced mycosis fungoides/Sezary syndrome. Ann Oncol 22:1608-1613, 2011
41. Mehta-Shah N, Lunning MA, Ruan J, et al: A phase I/II trial of the combination of romidepsin and lenalidomide in patients with relapsed/refractory lymphoma and myeloma. Hematol Oncol33:abstr 016, 2015 (suppl 1)
42. Mehta-Shah N, Moskowitz AJ, Lunning M, et al: A phase Ib/IIa trial of the combination of romidepsin, lenalidomide and carfilzomib in patients with relapsed/refractory lymphoma shows complete responses in relapsed and refractory T-cell lymphomas. Blood 128:2991, 2016
43. Horwitz SM, Koch R, Porcu P, et al: Activity of the PI3K-delta,gamma inhibitor duvelisib in a phase I trial and preclinical models of T-cell lymphoma. Blood 131: 888-898, 2017
44. Moskowitz AJ, Koch R, Mehta-Shah N, et al: In vitro, in vivo, and parallel phase i evidence support the safety and activity of duvelisib, a PI3K-δ,γ inhibitor, in combination with romidepsin or bortezomib in relapsed/refractory T-cell lymphoma. Blood 130:819, 2017 (suppl 1)
45. Odejide O, Weigert O, Lane AA, et al: A targeted mutational landscape of angioimmunoblastic T-cell lymphoma. Blood 123:1293-1296, 2014
46. Hamlin PA, Cheson BD, Farber CM, et al: The dual SYK/JAK inhibitor cerdulatinib demonstrates rapid tumor responses in a phase 2 study in patients with relapsed/refractory B- and T-cell non-Hodgkin lymphoma (NHL). J Clin Oncol36, 2018 (suppl; abstract 7511)

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Practical Treatment Approach for Angioimmunoblastic T-Cell Lymphoma

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