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Overview of T-cell Lymphomas

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Abstract

T-cell lymphomas are a mixed bag of diseases with a similar origin but diverse in biology and behavior. This review aims to highlight the key changes to the WHO classification and summarize the therapeutic paradigm as of the time of writing in November 2018.

Keywords: T-cell lymphoma, transplant

1. Introduction

T- and natural killer (NK)-cell lymphomas are a heterogeneous group of lymphoproliferative diseases that represent 10–15% of non-Hodgkin lymphomas (NHL). T-cell lymphomas in general have worse outcomes as compared to their B-cell counterparts. Over recent years, the understanding of the different subtypes of T-cell lymphoma has led to advances in management.

2. Background

2.1 WHO classification

T- and NK-cell lymphomas can be subclassified according to nodal, extranodal, cutaneous, or leukemic subtypes based on the 2008 World Health Organization (WHO) classification of lymphoid malignancies (Table 1) [1]. The 2016 update of the WHO classification saw the addition of three provisional entities and changes in designation to five entities, reflecting the advancements in the understanding of this group of diseases [2, 3]. The major changes are highlighted below.

The update in the classification saw follicular T-cell lymphoma coming under the umbrella of angioimmunoblastic T-cell lymphoma (AITL), given the common genetic mutations such as TET2, IDH2, DNMT3A, RHOA, and CD28 and fusions such as ITK-SYK and CTLA4-CD28 nodal peripheral T-cell lymphoma (PTCL), previously classified under peripheral T-cell lymphoma, not otherwise specified (PTCL NOS) was reclassified under the AITL classification given the similar genetic landscape.

The diagnosis of PTCL NOS is made when a lymphoproliferative disorder is of the T-cell lineage without any distinctive features that fit into the subtypes. Two distinct molecular subgroups have been identified in PTCL NOS with differing clinical outcomes and prognosis. High expression of transcription factor GATA3 was associated with worse clinical outcomes, while TBX2 expression enriched by IFNgamma and NfKB pathways was associated with better survival. These findings provide insight into a disease which has been a diagnosis of exclusion, with poor clinical outcomes and minimal advances in treatment.
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The ALK-negative subtype of anaplastic large cell lymphoma (ALCL) has been identified as a distinct entity. The expression of TNFRSF8, BATF, and TMOD1 differentiates ALK-negative ALCL from PTCL NOS. ALK-negative ALCL is a heterogeneous disease with a third harboring DUSP22 rearrangement and another 8% having TP63 rearrangements. The former has a 90% 5-year overall survival (OS) rate, mirroring the outcomes of its ALK-positive ALCL counterpart, while the latter is associated with a 5-year OS rate of 17%. The subset of ALK-negative ALCL which does not carry both the rearrangements has outcomes straddling in between these two extremes.

Breast implant-associated ALCL has been recognized as a provisional new entity—this is a unique variant in that the lymphomatous cells are confined to the seroma fluid surrounding the implant without capsular invasion. As such, surgical removal of the implant including the capsule is often curative, with systemic therapy being rarely indicated.

The 2008 classification included enteropathy-associated T-cell lymphoma (EATL) types 1 and 2 as part of the intestinal T-cell lymphoma spectrum. In the latest revision, this has been amended to EATL and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL). EATL is a condition linked to coeliac disease and is more common among northern Europeans. MEITL, on the other hand, is a disease of Asians and Hispanics with no associations with coeliac disease. At a molecular level, EATL is predominantly characterized by T-cell alpha/beta receptor expression, while MEITL has predominantly T-cell gamma/delta receptors being expressed. The nuclear expression of megakaryocyte-associated tyrosine kinase, MYC amplification, and alterations in SETD2 and JAK STAT pathways are other genetic events characteristic of MEITL [4].

2.2 Epidemiology

PTCL NOS forms about 25% of T-cell lymphomas, followed by angioimmunoblastic T-cell lymphomas (18%), NK-/T-cell lymphomas (NKTL—10%), and adult T leukemia/lymphoma (9%) [5]. Geographic variation in the various subtypes
of T-cell lymphoma has been reported. The international T-cell lymphoma study reported rates of PTCL and NKTL to be 5–10% in Western countries and 10–20% in Asian countries. However, Au et al., in a study of 148 patients, reported similar frequencies of T-cell lymphomas in the Western and Asian populations [6]. This was supported by another study analyzing the differences between PTCL and NKTL [7]. The perceived difference in the disparate frequencies of these diseases may have been contributed by a higher incidence of NKTL and adult T-cell lymphoma/leukemia (ATLL) in the Asian population.

3. Clinical aspects

3.1 Clinical characteristics

PTCL NOS is a disease of older adults with a median age of 60. It often presents at advanced stages with both nodal and extranodal sites of disease, with cutaneous and bone marrow involvement being the most common extranodal sites [5, 8].

Angioimmunoblastic T-cell lymphoma (AITL) is a multifaceted disease with a spectrum of clinical presentations, from fairly indolent disease to aggressive presentations. Similar to PTCL NOS, it is also a disease of older adults. Patients often present in advanced stages with B symptoms being the most common clinical manifestation. Bone marrow, liver, spleen, and skin involvements are common in this disease [9]. Immune-related phenomena such as hemolytic anemia, hypergammaglobulinemia, and positive Coombs test are associated with AITL [10].

Anaplastic large cell lymphomas (ALCL) are CD30-positive T-cell lymphoproliferative disorders with about half having ALK gene rearrangement (ALK + ALCL). The ALK-positive variant occurs in young adults with a median age of 30, while the ALK-negative ALCL is a disease of older adults. Systemic ALCLs have a varying clinical course and prognosis compared to their cutaneous counterparts, with the latter having an indolent course of disease with long-term survival in the range of 85–95% [11]. Central nervous system involvement is seen more commonly in ALCL than other T-cell lymphoma subtypes.

Extranodal NK-/T-cell lymphoma, nasal type, and aggressive NK-cell leukemia are the different subtypes of NKTL. NKTL commonly involves the nasal cavity and the upper aerodigestive tract. While localized disease is often treated with curative intent, advanced disease is invariably fatal. A small proportion of advanced NKTL patients can present with hemophagocytic syndrome resulting in high fevers, cytopenias, coagulopathy, abnormal liver function tests, and very high ferritin levels.

Adult T-cell leukemia/lymphoma is a disease of adolescents and young adults. Extensive marrow involvement defines the leukemic variant of this disease, while the lymphoma variant has less than 20% marrow involvement. This is a highly aggressive disease with common presentations including bulky mediastinal masses or nodal disease [12].

Cutaneous T-cell lymphoma (CTCL) is a heterogeneous group of disease, with mycosis fungoides and Sezary syndrome being the most common subtypes. The incidence of the various subtypes often increases with age [13]. CTCLs are generally indolent diseases, but large cell transformation is generally associated with poor outcomes [14].

3.2 Workup and diagnosis

Workup of T-cell lymphomas involves a complete history and physical examination followed by routine laboratory evaluation including full blood count, assessment
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of end-organ function, lactate dehydrogenase levels, and screening for human immunodeficiency virus, hepatitis B and C. Epstein-Barr virus (EBV) DNA testing using EBV PCR can be considered in EBV-positive tumors. Plasma EBV detection can serve as a marker to monitor disease response and as a prognostic factor in these settings [15]. Staging evaluations include radiological imaging and bone marrow biopsy [18]. Fluorodeoxyglucose positron emission tomography combined with computer tomography (PET CT) is gaining an increasing role in the initial staging of T-cell lymphomas. Given the high propensity for extranodal involvement, some of which (e.g., cutaneous involvement) may not be well demarcated on CT, PET CT may be useful as an initial staging modality. A retrospective study demonstrated that almost a third of the patients in the study had additional sites of disease picked up on PET CT beyond conventional CT imaging [16]. In NKTL, PET CT has been established as a standard staging investigation given its high sensitivity and specificity [17].

The diagnosis of T-cell lymphomas should ideally be made by a hematopathologist. An excisional biopsy is recommended whenever possible in order to ensure availability of adequate tissue sample for histopathological analysis. According to the WHO classification in 2008, the diagnosis of PTCL requires the integration of clinical, pathological, immunohistochemical, and molecular findings.

4. Management

At present there is no standard of care available for management of T-cell lymphoma as a result of paucity of randomized controlled phase 3 trials. Anthracycline-based regimens such as cyclophosphamide, vincristine, doxorubicin, and prednisolone (CHOP) have been the backbone of treatment for many decades for most subtypes of T-cell lymphomas, with the exception of NKTL. The international T-cell lymphoma project, with a predominant European and Asian population, demonstrated that there was no survival benefit seen with an anthracycline-based regimen for PTCL NOS and AITL [5]. A subsequent retrospective study in a north American population showed 25 months improvement in survival with the use of an anthracycline-based regimen, even after controlling for confounding factors [18]. Nevertheless, unlike the B-cell counterparts, T-cell lymphomas in general have a poorer outcome, with 5-year overall survival being about 30%.

In NKTL, anthracycline-based regimens were abandoned early on with the discovery that NK cells have a high expression of multidrug-resistant P-glycoprotein. Hence, drugs that are transported by P-glycoproteins such as cyclophosphamide and doxorubicin become ineffective [19]. L-asparaginase is an enzyme that induces cytotoxicity to lymphoma/leukemic cells by catalyzing the hydrolysis of L-asparagine, thereby resulting in its depletion. This drug has been demonstrated to have significant in vitro activity against NK cells [20] and hence has been incorporated into the treatment regimens. Hence, in advanced NKTL, L-asparaginase-based multiagent chemotherapy has been adopted as first-line treatment.

4.1 Strategies to improve first-line treatment

4.1.1 Intensive chemotherapy

Multiple strategies have been explored in order to overcome the poor treatment outcomes in T-cell lymphomas. A retrospective study by MD Anderson group demonstrated that more intensive regimens such as HyperCVAD and HyperCHOP did
not fare better than conventional CHOP in non-ALCL T-cell lymphomas. The 3-year overall survival was 49% in the intensive treatment group as compared to 43% in the CHOP group, and this was not statistically significant [21].

The GOELAMS-LTP95 was a phase 3 randomized trial that compared alternating cycles of VIP and rABVD (etoposide, ifosfamide, cisplatin—VIP; reinforced adriamycin, bleomycin, vinblastine, dacarbazine—rABVD) against CHOP for non-cutaneous T-cell lymphomas. There was no significant difference in the 2-year event-free survival, which was the primary endpoint of the study [22].

Gemcitabine, cisplatin, and methylprednisolone were compared to CHOP in the treatment of T-cell lymphomas in the first-line setting in a phase 2 trial. This CHEMO-T trial did not show any improvements in complete response rates, progression-free or overall survival rates between four cycles of GEM-P and six cycles of CHOP [23].

Hence, intensifying first-line chemotherapy as a strategy has not improved outcomes in T-cell lymphomas.

### 4.1.2 Addition of etoposide

The NHL B1 and B2 studies were designed to answer the questions of whether addition of etoposide to CHOP or increasing dose intensity of CHOP will improve outcomes in patients with aggressive lymphomas. T-cell lymphoma patients formed 13.7 and 5.8% of the study populations in NHL B1 [24] and B2 [25] studies, respectively. In young patients, addition of etoposide improved event-free survival by about 10%, but this did not translate into improvement in overall survival. In older patients, the addition of etoposide did not improve progression-free or overall survival compared to CHOP which became the German standard of care following the NHL B2 trial.

A retrospective review of patients treated in trials designed by the German non-Hodgkin lymphoma study group showed an improvement in 3-year event-free survival (EFS) from 51 to 75.1% (p = 0.03). However, this difference in EFS was predominantly contributed by the ALK-positive ALCL—the EFS in this subgroup improved markedly from 57.1 to 91.2% with the addition of etoposide. The difference in EFS was no longer statistically significant when this group was removed from the analysis [26].

Similar results were noted in a retrospective study by a Swedish group which analyzed 755 patients with T-cell lymphoma. Improvement in EFS was seen without a corresponding survival benefit [27].

A large retrospective study of 1933 Korean patients with T-cell lymphomas concluded that addition of etoposide had no progression-free or overall survival benefit, even in younger patients with good performance status. About 17% of the study population consisted of ALCL patients, but there was no differentiation between the ALK-positive and negative subtypes [28].

In summary, the benefit of etoposide comes through predominantly in the ALK-positive ALCL group. For the rest of T-cell lymphomas, etoposide is likely, and active agent and addition of this drug in younger patients remain an option, as long as toxicity can be minimized.

### 4.2 Role of upfront autologous transplant as consolidation

The PARMA study established the role of high-dose chemotherapy and autologous peripheral stem cell transplant (HDC and APSCT) in relapsed refractory B-cell lymphomas. Given the poor outcomes of T-cell lymphomas, this option was explored in T-cell lymphomas.
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One of the earliest prospective studies addressing the role of upfront APSCT in T-cell lymphoma was reported by Corradini et al. [29]. This Italian study reported long-term outcomes of two prospective phase 2 studies of patients with T-cell lymphoma treated with upfront HDC and APSCT. Sixty-two patients with stage 2 to 4 T-cell lymphoma underwent two different conditioning regimens. Thirty percent of these patients had ALK-positive ALCL. Seventy-four percent of the patients underwent HDC and APSCT. Twelve-year overall survival and event-free survival with APSCT were 37 and 25%. ALK-positive ALCL patients had a significantly better survival than their other T-cell lymphoma counterparts. Achieving complete remission (CR) before APSCT was a strong predictor of improved survival in this study. Patients who achieved a CR before transplant had a 12-year DFS of 60% [29].

In another prospective single-arm study, 83 patients with PTCL, AITL, and ALK-negative ALCL as the predominant histologies were treated with 4–6 cycles of CHOP followed by HDC and APSCT. The 3-year OS and PFS were 48 and 36%, respectively. Eighty percent of patients relapsed within 24 months from APSCT [30].

The Nordic lymphoma group conducted a phase 2 prospective trial of 160 patients with T-cell lymphoma, to determine the outcomes of dose-dense chemotherapy followed by HDC and APSCT. Patients were treated with three cycles of CHOPE (cyclophosphamide, doxorubicin, vincristine, prednisolone, and etoposide) every 14 days. In patients older than 60, etoposide was omitted—hence patients received dose-dense CHOP. Those who had partial or complete responses (PR or CR) went on to receive three more cycles of the same chemotherapy regimen followed by HDC and APSCT. Of note, ALK-positive ALCL patients were excluded. PTCL NOS patients were 39% of the cohort, followed by AITL and ALK-negative ALCL, each consisting of 19%. About 70% of patients underwent HDC and APSCT. The 5-year OS and PFS were 51 and 44%, respectively. The ALK-negative ALCL group had the highest 5-year OS of 70%. Toxicities of the dose-dense regimen were however not insignificant. Grades 3 and 4 hematological and non-hematological toxicity rates were 86 and 45%, respectively, with a treatment-related mortality of 4% [31].

While these studies seem to suggest a better outcome with upfront HDC and APSCT, compared to historical controls, the lack of a randomized comparison between upfront HDC and APSCT and conventional chemotherapy alone makes it difficult to establish this as standard of care. Given the absence of randomized trials, HDC and APSCT in first clinical remission (CR1) has been incorporated into guidelines. However, recent data is emerging to suggest that patients in CR1 may actually not benefit from HDC and APSCT.

A retrospective review of 105 patients who received CHOP-based chemotherapy as first-line was done. About 52.1% of the study population were in CR1. About half of these patients underwent HDC and APSCT, whereas the other half were on surveillance. At 22 months, the median PFS of the surveillance group compared to the group that underwent transplant was 15.8 months vs. 12.8 months, but this was not statistically significant. The authors hence concluded that patients who are in CR1 following induction chemotherapy may not benefit from APSCT [32].

Our group did a retrospective analysis of 175 patients from Singapore, South Korea, and China. PTCL NOS patients formed 42% of the cohort. AITL and ALK-negative ALCL formed 33% and 22% of the cohort, respectively. About 92% of patients received anthracycline-based induction chemotherapy. However, only 18% of the cohort underwent upfront HDC and APSCT. Median PFS was 5.5 years for the entire population but OS was not reached. On multivariate analysis, age and advanced stage of disease were identified as poor prognostic factors. The use of anthracycline-based regimens as well as HDC and APSCT did not feature as significant factors affecting survival or progression-free survival outcomes, even in younger patients [33].
These results were echoed in a multicenter retrospective study done in Europe. AITL was the most common subtype in this dataset (46%), compared to PTCL NOS (29%) and ALK-positive ALCL (25%). In order to eliminate selection bias in the retrospective analysis, multivariate proportional hazard model and propensity score matching model were both applied. Two-hundred sixty-nine patients were analyzed among whom half the patients had undergone HDC and APSCT at CR1 and the other half was under surveillance. Five-year PFS and OS were 45% and 60%, respectively, for the overall population. Consolidation APSCT at CR1 did not improve survival outcomes in this population. Once again, remission status (CR or PR) at the end of induction featured as a significant prognostic factor [34].

In summary, achieving a CR at the end of induction therapy is a crucial prognostic factor in determining outcomes in TCL. The role of upfront autologous transplant, especially in patients who have achieved CR1, remains to be defined.

4.3 Role of allogenic transplant in CR1

Two prospective studies attempted to explore the role of allogenic transplant in first remission [35, 36]. In both the studies, about 39% of patients did not undergo transplant, predominantly due to early progression. In the Italian study, only a quarter of the patients who underwent transplant remained in CR at 44 months. Hence, allogenic transplant as consolidation therapy is not recommended.

4.4 Relapsed or refractory disease

In the relapsed setting, autologous or allogenic transplant remains as options following salvage chemotherapy to attain a response. The Center for International Blood and Marrow Transplant Research reported 3-year PFS and OS rates of 41 and 53%, respectively, for patients undergoing autologous transplant at first relapse. The rationale for allogenic transplant in lymphoma has been to harness the graft versus lymphoma effect. Three-year OS for myeloablative versus a non-myeloablative regimen was 31 and 50%, respectively. Once again, having a chemosensitive disease and having two lines of treatment or fewer were important prognostic factors for survival [37, 38].

4.5 Novel agents

4.5.1 Brentuximab vedotin

Brentuximab vedotin is an antibody-drug conjugate (ADC) composed of a chimeric monoclonal antibody linked to an anti-tubulin agent, monomethyl auristatin E (MMAE). The monoclonal antibody targets CD30-expressing cells, and MMAE is released intracellularly to bind to tubulin. The binding of MMAE to tubulin disrupts the microtubule network, causing cell cycle arrest and apoptosis. Brentuximab vedotin is cell cycle phase-specific (G2/M phase). CD30 is uniformly expressed in anaplastic large cell lymphomas. In addition to that, about 43% of PTCL (excluding ALL) has been estimated to have CD30 expression [39].

A phase 2 study demonstrated a response rate of 41% when brentuximab was administered to CD30-positive T-cell lymphomas, at 1.8 mg/kg every 3 weeks. This study excluded ALCL patients. This was a considerable response given that 63% of patients were refractory to the most recent therapy prior to brentuximab. Interestingly, the degree of CD30 expression did not correlate with the responses [40].

A retrospective French study analyzed the effectiveness of brentuximab in 56 patients. Twenty-four patients had ALCL. Cutaneous lymphomas (72%) and
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ALCLs (62%) had better overall response rates than non-ALCL PTCLs (21%). Contrary to the study by Horwitz et al., this study reported a statistically significant improvement in PFS with stronger (>75%) expression of CD30 [41].

A prior study in JCO reported exceptional response rates of 86% with the use of brentuximab in relapsed refractory ALCL. The CR rates were 57% and median duration of response was 12.6 months. These excellent responses were demonstrated despite 62% of patients having primary refractory disease [42].

The ALCANZA trial was a phase 3 trial that compared brentuximab against physician choice treatment for patients with cutaneous T-cell lymphomas who have seen prior treatment. This study demonstrated that patients who had brentuximab had better objective global response rates (56.3%) than those who had physician choice treatment (12.5%). The endpoint of objective global response comprised of response in the skin, node, viscera, and blood, lasting for a minimum of 4 months. The median progression-free survival was 16.7 months vs. 3.5 months HR 0.27 (p < 0.0001). These results are certainly promising, especially given that this group of diseases has limited efficacious systemic treatment [43, 44].

The efficacy of brentuximab in the relapsed refractory settings has prompted the evaluation of this drug in the first-line setting. A phase 1 study explored the safety and efficacy of combining brentuximab with cyclophosphamide, doxorubicin, and prednisolone (BV CHP) in 26 treatment naïve PTCL patients. Patients received six cycles of BV CHP followed by BV maintenance for up to 10 cycles. Seventy-three percent of the study population consisted of ALCL. One hundred percent response rate with 50% continuing to remain in CR at 5 years was reported. The predominant toxicity was peripheral neuropathy which resolved in the majority. While the results are exciting, it is possible that the results were driven primarily by the ALCL population. A larger randomized study stratified by tumor subtypes will be important before this is adopted as the new standard of care [44].

Regardless, the promising efficacy of brentuximab, at least in the post first-line setting cannot be disregarded. This is generally a well-tolerated drug with predominant toxicities being peripheral neuropathy, myelosuppression, fatigue, and nausea.

4.5.2 Pralatrexate

Pralatrexate is a novel antifolate drug which inhibits dihydrofolate reductase enzyme, thereby inhibiting the conversion of dihydrofolate to tetrahydrofolate. Blocking this essential step in DNA and RNA synthesis results in cell cycle arrest. In addition, its high affinities for reduced folate carrier and folicpolyglutamate synthase are distinctive features that account for its superior activity compared to other drugs in the same class [45]. The early phase II-I-II study showed an overall response rate of 54% in TCL, compared to only 5% in B-cell lymphomas [46]. A weekly dose of 30 mg/m² for 6 out of 7 weeks had a better toxicity profile than a dose of 135 mg/m² given every other week. The PROPEL study which recruited 115 patients with TCL demonstrated an overall response rate of 29%. Eleven percent achieved CR. Of note, 5 out of 26 patients who were refractory to prior lines of therapy responded to this drug [47]. However, common toxicities of this drug include mucositis, fatigue, myelosuppression, and abnormal liver function tests.

4.5.3 Romidepsin

Romidepsin is predominantly a class 1 histone deacetylase inhibitor (HDAC). Through complex interactions, which remain to be fully understood, this drug disrupts chromatin structure and activates transcription factors. As a result, it mediates cell cycle arrest and cell death and increases transcription of tumor suppressor
genes. In a pivotal phase 2 study, romidepsin was administered at 14 mg/m\(^2\) on days 1 and 8 and 15 in a 28 days cycle, to patients with relapsed or refractory T-cell lymphoma. PTCL and AITL were the most common subtypes in the study. A 25% response rate was reported, with 15% achieving CR. Responses were also durable with median duration of response being 17 months [48]. Another phase 2 study by the NCI group reported 38% response rates with duration of response being 8.9 months [49]. The main toxicities in both these studies were cytopenias, infections, fatigue, and nausea.

4.5.4 Belinostat

Belinostat is a pan-HDAC inhibitor which inhibits classes I, II, and IV HDAC. It facilitates apoptosis and cell cycle arrest in abnormal, transformed cells through complex interactions with cell cycle mechanisms. Based on a phase 2 trial which demonstrated 25% response rates in PTCL, the BELIEF (Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma) trial was conducted. This was a single-arm study where belinostat was administered as an intravenous infusion at a dose of 1000 mg/m\(^2\) on days 1–5 Q21 days, to patients with relapsed or refractory T-cell lymphomas. The study reported a modest objective response rate of 26% with duration of response of 8.3 months. Of note, AITL patients had a higher response rate of 46% than 23% in PTCL patients. The main toxicities were fever, hematological toxicities, nausea, and fatigue [50].

5. Conclusion

T-cell lymphoma has evolved from being one disease to a mixed bag of multiple diseases, each of which is being understood at greater depths now, with the advent of technology and molecular biology. With a better understanding of the disease biologies, the therapeutic armamentarium needs to be developed further in order to improve outcomes from these diseases.

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