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Management of T-Cell Lymphomas: Overcoming Challenges and Choosing the Best Treatment

The T-cell lymphomas (TCLs) are heterogeneous group of lymphoid neoplasms populated with cells derived from either precursor or post-thymic mature T cells. The mature T-cell neoplasms arising from the post thymus are further classified into several subtypes based on World Health Organization (WHO) classification. Conventionally, TCLs are categorized as peripheral or cutaneous, the latter usually associated with a prolonged median survival. TCLs account for approximately 10%–15% of all non-Hodgkin lymphomas (NHLs) in Caucasians. The prevalence is higher in Asia. Certain subtypes are almost uniquely more common in Southeast Asia, with a rare occurrence in North America.[1–3] In North America, peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL), and angioimmunoblastic T-cell lymphoma (AITL) together represent two thirds of all mature TCLs. In Asia, however, extranodal natural killer (NK)/T-cell lymphoma, nasal type accounts for the majority of mature TCLs

As oncologists, we are confronted with difficult challenges in the diagnosis and treatment of TCL and more often than not are faced with unsatisfactory outcomes. In this issue of *Seminars in Hematology*, experts in the field have contributed to discuss the pathological classification, treatment options including novel therapies and rare TCLs that are approached uniquely.

DIAGNOSIS AND OUTCOME DATA

Similar to B-cell lymphomas, diagnosis of TCLs includes an array of immunohistochemical staining. Clonal rearrangements of the T-cell receptor (*TCR*) gene are helpful in making the diagnosis. The WHO classification integrates morphologic, immunophenotypic, genetic, and clinical features to ascertain the subtype of T-cell lymphoma. The rarity of this disease in clinical practice and the complexity involved with immunophenotypic characterization may lead to misdiagnosis and inferior or unnecessary treatment. It may thus be helpful to obtain the opinion of an expert hematopathologist when confronted with the rare T-cell entity.[4]

Patients with anaplastic lymphoma kinase (ALK)-positive variants of ALCL have better outcomes, with 5-year survival rates of 70%. In contrast, survival sequentially declines for ALK-negative ALCL (49%), PTCL-NOS (32%), and AITL (14%).[5] There are few reports on the clinical outcome of large numbers of patients with TCLs.[6–8] Most importantly, if we consider studies that include patients based on modern classification incorporating genetic features then the reported studies are much fewer in number. This would therefore influence distinguishing prognostic variables. In most of the previously reported studies, outcome was based on heterogeneous treatments comprising of different modalities that may vary from steroids to stem cell transplantation. With the exception of extranodal NK/T-cell lymphoma, clinical trials have included several histologies, thus making definite treatment guidelines for each subtype complex.

THERAPEUTIC CHALLENGES

Indolent TCLs, such as mycosis fungoides, typically have a prolonged clinical history with relapses and remissions. Aggressive TCLs, on the other hand, usually present with a fulminant clinical course and are associated with a shorter survival. A recently recognized entity that is worth mentioning are the indolent T-cell lymphoproliferative disorders of the gastrointestinal tract. Presenting symptoms include nausea, diarrhea, dyspepsia, and malnutrition with dense infiltrates involving the oral mucosa, stomach, small intestine, and colon. Despite the clinical scenario mimicking that of a malignant course, this disease does not respond to traditional chemotherapy.[9] Therefore careful interpretation of pathological data is crucial.

INITIAL THERAPY FOR T-CELL LYMPHOMAS

In contrast to the progress made in the treatment of aggressive B-cell lymphoma, evidence for similar therapeutic

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improvements in TCLs is lacking. There have been fewer prospective trials comparing different induction regimens in the treatment of mature TCLs. The combination chemotherapy CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) has become the most frequently used regimen mainly because of the ease of administration, as extrapolated from the treatment of aggressive B-cell lymphomas.[10] With the exception of ALK-positive ALCL, the response of TCLs to CHOP is much less satisfactory than that of the B-cell lymphomas, with a response rate of approximately 60% and a 5-year overall survival (OS) of 30%.[1] Intensive chemotherapies have not been proven superior to CHOP in terms of survival.[11,12] In younger patients, however, addition of etoposide to CHOP (CHOEP) might improve progression free survival (PFS), but OS remained unchanged.[5] Thus, CHOP as the backbone is still the standard initial treatment of TCLs, despite the un-encouraging outcome. Aggressive TCLs respond poorly to anthracycline-based chemotherapy. One hypothesis is that the overexpression of P-glycoprotein (Pgp), confers increased chemo-resistance of lymphoma cells.[13] L-Asparginase-based chemotherapy, which is not affected by Pgp, has been shown to be a superior regimen than CHOP-based therapy in NK/T-cell lymphoma.[14]

As our understanding of the pathogenesis and molecular pathways for the basis of TCLs improves, the development of newer chemotherapy, drug delivery and novel agents targeting specific metabolic pathways will continue to make progress. Current research should emphasize on novel combination therapies and moving beyond CHOP chemotherapy in an international effort.

MANAGEMENT OF DISEASE RELAPSE

In the absence of hematopoietic stem cell transplantation (HSCT), treatment of relapsed or refractory TCL is usually palliative. A number of novel therapies are currently under investigation for relapsed and refractory disease. Since, 2009, the US Food and Drug Administration has approved three novel therapies specifically for its use in TCLs based on overall response rates and duration of response: pralatrexate (Folotyn; Allos Therapeutics, Lexington, MA), romidepsin (Istodax; Celgene, Summit, NJ), and brentuximab vedotin (SGN-35; Seattle Genetics, Bothell, WA).[15] These agents are quickly making their way towards upfront therapy in clinical trials. Nevertheless, as a single drug, these agents are not curative. Combination of these agents might be more efficacious and should be carefully evaluated in future studies.

Dedicated clinical trials for each histological subtype can be accomplished with international collaboration. Until then an ongoing challenge for the treating physician is to understand and interpret the results of the clinical trial with caution and caveats so as to avoid exposing our patients to unnecessary treatments.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Attempts to improve outcomes have included autologous or allogeneic HSCT.[7,8] Single-institution studies and retrospective analyses suggest that both modalities lead to durable remissions in recurrent disease settings and might be important in consolidating first remission. However, key questions remain, including identification of optimal populations, relative efficacy of autologous versus allogeneic approaches, and HSCT timing (first-line consolidation v relapse). Although autologous or allogeneic HSCT may offer a cure to some of the patients, a substantial proportion of patients are not eligible for transplantation because of the chemotherapy refractoriness or short remission duration of the lymphomas after initial chemotherapy. Novel therapies may open up the potential path for better disease control pre-HSCT.

UPFRONT TRANSPLANTATION

In view of the high relapse rate in the majority of TCLs, high-dose chemotherapy with autologous HSCT has been attempted in first remission to improve treatment outcome. Several prospective and retrospective studies have shown an improved survival in patients treated with auto-HSCT in first remission.[7] In one of the largest prospective trials involving 166 patients with TCLs, the estimated OS and PFS were 51% and 44%, respectively.[16] When stratified according to histologic subtypes, ALK-negative ALCL patients achieved highest survival rate with 5-year OS and PFS 70% and 61%, respectively. A major limitation of this approach, however, is that a significant proportion of patients will fail to respond to induction chemotherapy or have early disease progression, thus precluding HSCT. Across all retrospective and prospective trials that have addressed the role of auto-HSCT in TCLs, the procedure is considered safe and feasible, but unfortunately resulted in unavoidable poor outcome in chemorefractory disease.[7]

The role of frontline auto-HSCT remains to be fully delineated. We currently do not know if achieving complete remission (CR) versus partial remission (PR) before transplant, or normalized functional imaging significantly improves long-term outcome. All the prospective trials of upfront auto-HSCT demonstrated that chemosensitive disease is the strongest predictor of outcome thus the emerging key message is that only chemosensitive disease seems to benefit from autografting and that there is no reason to perform auto-HSCT in refractory patients. In addition due to the absence of phase III trial we do not know for sure if patients in CR really need a consolidation with auto-HSCT.[7,17]

Early progressive disease after induction treatment, that entail about one third of patient, is the major limitation to proceed with transplant and represents a treatment failure with currently no alternative effective strategies.[18] In this