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Non-Hodgkin Lymphoma – State of the Art and Next Questions

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The diseases we call non-Hodgkin lymphoma represent a wide variety of pathological and clinical entities. With developing insights into the biology of these disorders they are being divided into increasingly uniform subgroups requiring specific treatment approaches. Treatment results have steadily improved and for most subgroups there is some chance for cure with available treatments.

Diagnosis, Staging, and Restaging

The 2016 WHO classification system for non-Hodgkin lymphoma includes more than 60 definite and provisional entities (table 1).[1] The specific diagnosis of a subtype of non-Hodgkin lymphoma remains a difficult task for pathologists. The pathologist needs to take into account immunological and genetic information in addition to morphology. Often the pathologist will benefit from having clinical information about the patient. The diagnosis is best reached when an adequate, usually excisional, biopsy is analyzed by an expert in lymphoma pathology.

As with most malignancies, a careful staging evaluation is key to planning therapy. For most types of non-Hodgkin lymphoma a PET/CT scan is a key component of this evaluation. When a PET/CT scan is not available, or the patient has one of the subtypes of non-Hodgkin lymphoma that are often PET negative, a chest, abdomen and pelvic CT scan is utilized. The post treatment evaluation, or restaging, of patients with non-Hodgkin lymphoma is best accomplished with repeating the PET/CT scan in patients with a PET avid lymphoma. The availability of the Deauville score (table 2)[2] has standardized post treatment evaluation. The best definition of a complete remission appears to be achievement of a score of Deauville 3 – something that has been well documented in patients with diffuse large B-cell lymphoma and follicular lymphoma, but probably also applies to other PET avid lymphomas.[3,4]

At the present time, there is considerable enthusiasm for early, or interim, restaging. Usually done after 1-3 cycles of therapy, the goal is to identify patients with very responsive tumors in whom treatment might be shortened or reduced in intensity, and those patients with more resistant tumors in which treatment might be intensified or changed. While there is increasing data to utilize this approach in patients with Hodgkin lymphoma, it has been more difficult to apply this approach for patients with non-Hodgkin lymphoma and most attempts have not shown any therapeutic advantage. Even when an interim PET/CT is done, it is important to remember that

the best predictor of a good outcome after therapy is a negative PET/CT at the completion of treatment.

In several types of non-Hodgkin lymphoma there have been specific prognostic indices derived to help predict treatment outcome and make treatment decisions. The IPI score is widely used in diffuse large B-cell lymphoma, but can apply to other subtypes.[5] Specific systems have been derived for follicular lymphoma, mantle cell lymphoma, and the peripheral T-cell lymphomas.[6,7,8]

New Insights in Managing Specific Subtypes

Diffuse large B-cell lymphoma

The majority of patients with diffuse large B-cell lymphoma can be cured with currently available treatments. While CHOP-R has been the standard therapy in much of the world for many years, there has been enthusiasm for the use of the infusional regimen EPOCH-R in the United States. However, a recent intergroup trial was just completed that failed to show an advantage for EPOCH-R, although subgroup analyses have not all been completed.[9] In France, ACVBP-R has been utilized in younger patients and showed a progression free survival advantage.[10] However, this regimen is not utilized in the United States.

It has been known for many years that patients whose diffuse large B-cell lymphoma is classified as activated B-cell subtype on gene expression profiling have a worse prognosis than patients whose lymphoma is classified as germinal center B-cell subtype.[11] A variety of regimens including the more intensive regimens ACVBP-R and EPOCH-R along with newer approaches such as adding lenalidomide or ibrutinib to CHOP-R might be better for lymphomas classified as the activated B-cell subtype. Studies are currently ongoing.

A very poor prognosis subtype of diffuse large B-cell lymphoma has gene rearrangements of both the BCL2 gene and the MYC gene and are almost always of the germinal center B-cell subtype.[12] Patients with the activated B-cell subtype sometimes have rearrangements of the MYC gene and the BCL6 gene and also have a poor prognosis. These are often called double hit lymphomas. It is not yet clear that a particular treatment regimen is able to overcome the poor prognosis associated with double hit diffuse large B-cell lymphoma, although patients are usually treated with more intensive regimens. Patients with the activated B-cell subtype frequently over express both MYC and BCL2 protein (i.e., referred to as double expressers) and these tumors are associated with a somewhat poorer prognosis than patients who don't over express the proteins, but better than seen with double hit lymphomas.[13]

Patients with diffuse large B-cell lymphoma who fail primary therapy and who continue to have chemotherapy sensitive tumors can sometimes be cured with autologous bone marrow transplantation. This remains the treatment approach with the documented highest chance for cure in this setting. However, chimeric antigen receptor T-cells are active in this setting and might replace bone marrow transplantation as a treatment of choice for some or all of these relapsed patients.[14]

Follicular lymphoma

The survival of patients with follicular lymphoma has improved dramatically since the availability of rituximab. Today the median survival of patients with low grade follicular lymphoma is in the range of 15-20 years. In the United States most patients with low grade follicular lymphoma who require therapy (i.e., some asymptomatic patients are still observed without therapy) will receive single agent rituximab, bendamustine combined with rituximab, or CHOP combined with rituximab. It is not clear that either of the two chemoimmunotherapy regimens is superior to the other, although bendamustine with rituximab is currently more widely utilized. A recent study suggested that substituting obinutuzumab for rituximab in the chemoimmunotherapy regimen associated with a better progression free, but not overall survival when maintenance antibody therapy is utilized.[15] Maintenance antibody therapy with rituximab has been widely utilized after induction therapy and prolongs progression free survival. Whether or not it prolongs overall survival remains a point for debate.

Multiple new drugs have been shown to be active in follicular lymphoma including lenalidomide, venetoclax, idelalisib, ibrutinib, and PD-1/PDL-1 inhibitors.[16,17,18] The combination of lenalidomide and rituximab has been shown to be highly active and might become a standard initial therapy for this disease.[17]

Patients with high grade follicular lymphoma should be treated with the same regimens as utilized in diffuse large B-cell lymphoma. Today pathologists try to make a distinction between low and high grade follicular lymphomas by calling the latter group grade 3B follicular lymphoma.

Mantle cell lymphoma

Treatment outcome for patients with mantle cell lymphoma has improved considerably in the last 20 years and continues to evolve. The CHOP-R regimen with bortezomib substituted for vincristine is highly active.[19] Bendamustine and rituximab is widely utilized as are regimens that include high dose cytarabine and those that include lenalidomide. [20,21] All these appear superior to CHOP-R. Ibrutinib is highly active in mantle cell lymphoma and is frequently utilized as treatment after relapse.[22]

Burkitt lymphoma

Burkitt lymphoma has a high cure rate with very intensive, short course regimens such as CODOX-M/IVAC and hyper CVAD.[23,24] However, these are not always well tolerated, particularly by older patients. A similar cure rate appears achievable utilizing EPOCH-R and this is better tolerated in older patients.[25] All patients with Burkitt lymphoma should receive CNS prophylaxis.