key note lectures

001 DIFFUSE LARGE B-CELL LYMPHOMA: WHICH TREATMENT FOR PATIENTS WHO FAILED FIRST LINE TREATMENT?

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The introduction of rituximab, a monoclonal antibody targeting CD20, has completely modified the treatment of B-cell lymphomas, particularly diffuse large B-cell lymphomas (DLBCL). As demonstrated in several randomized studies, the combination of rituximab and CHOP regimen increases complete remission (CR) rates, decreases relapse rates, and prolongs duration of response and survival when used as first line therapy in DLBCL patients. If this allowed increasing the cure rate in all subgroups of DLBCL patients, not all benefit from this improvement. In good risk patients as defined by the International Prognostic Index (IPI), long-term progression-free survival (PFS) and overall survival (OS) are usually over 80% but for poor-risk patients they are only approaching 40%. As with chemotherapy only, only patients who reached CR may be cured and salvage stays a difficult problem for progressing patients. Among failing patients, 3 groups with different outcome may be described: refractory patients, not responding to 1st line therapy; partial remitters (PR), with persisting lymphoma sites at the end of treatment; relapsing patients, with progressive disease after CR. Usually these 3 groups were lumped together and studies are presented on 'refractory-relapsing' patients. However, the outcome is quite different and the mechanisms leading to this refractoriness to chemotherapy are probably quite different too. The only way to improve outcome of these difficult patients is to look at them separately and prospectively. A review of these different situations and solutions to improve outcome will be presented. Current treatments of these patients associate salvage chemotherapy followed with high-dose therapy and autologous transplant in young patients. For elderly patients, outcome is poorer because the toxicity preventing the use of high-dose therapy. Improvements may only come from the description of clinical and biologic parameters associated with these conditions. The best solutions will come from recognition of the potential refractoriness before beginning treatment and to modify the standard R-CHOP regimen to improve response, at least for refractory and PR patients. Maintenance therapy after CR might also be a solution for relapsing patients. Among new drugs, targeted therapies, monoclonal antibodies or small molecules, might be a solution but the current search in these promising possibilities is mainly directed to rare entities like mantle cell lymphoma or peripheral T-cell lymphoma.

002 THE ROLE OF THE MICROENVIRONMENT IN LYMPHOMA BIOLOGY

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Much of the focus and attention for cancer biology over the past many years has been devoted to comprehensively understanding the genetic alterations that characterize the neoplastic cells in non-Hodgkin lymphoma (NHL) biopsies. Specific translocations, copy number alterations, loss of heterozygosity and a plethora of other genetic aberrations deregulate critical pathways in the malignant cells, ultimately conferring a growth and/or survival advantage. More recently, attention has turned to a careful examination of the composition and function of non-neoplastic cells resident within these tumoral tissues. As has been shown for many solid tumors, active crosstalk between neoplastic cells and a variety of specific non-neoplastic cells in the microenvironment can be demonstrated in several NHL subtypes, including follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL). Cells implicated in the microenvironment include reactive T cells, regulatory T cells, benign B cells, macrophages, dendritic cells, fibroblastic reticular cells and endothelial cells that comprise the vascular bed of these tumors. The lymph node (LN) signature in DLBCL was recognized several years ago as an important contributor to patient survival. The precise cellular constituents of this stromal gene signature and how it functions to confer a favorable outcome in patients is still the matter of on-going studies that will be presented. FL is a tumor that recapitulates the normal secondary lymphoid follicle and is rich in tumor cell-microenvironment interactions. FL cells are almost impossible to grow *in-vitro* and show a strong dependency on both stromal and immune-related cells. A number of non-neoplastic cells have been implicated and their impact on survival may be associated with both treatment and patient characteristics. Some data suggest that FL may be dichotomized into two major groups, one largely driven by tumor cell genetics and the other heavily influenced by microenvironmental interactions. Specific support for this hypothesis will be discussed. Lastly, data will be presented to highlight the role of the microenvironment in determining the clinical behavior and response to therapy in patients with cHL. Specifically, the role of Hodgkin Reed-Sternberg cells in shaping their milieu will be discussed.

003 ARE WE CHANGING THE NATURAL HISTORY OF FOLLICULAR LYMPHOMA?

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For decades many oncologists treating patients with lymphoma have felt that the overall survival of patients with follicular lymphoma was not significantly impacted by therapy. It was clear that available treatments could cause remissions, but patients usually relapsed during the first few years and their lymphomas typically remained chemotherapy sensitive. Patients who were not seriously ill were often followed without therapy with no evidence that this adversely impacted outcome. The few randomized trials comparing no therapy with immediate treatment, or minimal versus more intensive therapy, did not show any survival advantage. Recent reports suggest that the prognosis for patients with follicular lymphoma is changing. The SEER data base in the United States follows population based data and reported an improved survival for patients diagnosed with follicular lymphoma in the 1990's as opposed to those diagnosed in the preceding decade. Both the Southwest Oncology Group and investigators at MD Anderson have observed an improvement in survival for patients participating in sequential therapeutic trials for follicular lymphoma—most striking after the incorporation of monoclonal antibodies into treatment regimens. A meta-analysis of the use of interferon in the treatment of patients with follicular lymphoma found that survival improved significantly in high risk patients who were treated aggressively with standard chemotherapy regimens in addition to adequate doses of interferon. Follicular lymphoma is a complicated disease. The host/lymphoma relationship is important as illustrated by frequent spontaneous regressions in patients who are followed without therapy and the responses that have been seen secondary to the graft-versus-lymphoma effect of allogeneic hematopoietic stem cell transplantation. Gene expression profiles in follicular lymphoma suggest that the host immune response might be more prognostic than the genetic changes in the tumor cells. Some follicular lymphomas have a high proportion of large, "blast" cells and frequently have durable remissions induced by anthracycline containing chemotherapy regimens. Low grade follicular lymphomas frequently transform to diffuse large B-cell lymphoma (more than 50% in some autopsy series) and this is often, but not always, a harbinger of short survival. Recent reports have suggested that the risk of transformation might be reduced by initial therapy with anthracycline containing combination chemotherapy regimens. The survival of patients with follicular lymphoma seems to be improving but there is still considerable room for improvement. Understanding which patients are particularly likely to benefit from one of the available therapies, which subgroups might be curable, and if there is still a subgroup of patients for whom watchful waiting is the best initial approach remain important questions.