BIOLOGY

002 THE ROLE OF THE MICROENVIRONMENT IN LYMPHOMA

possibilities is mainly directed to rare entities like mantle cell lymphoma or peripheral
small molecules, might be a solution but the current search in these promising
relapsing patients. Among new drugs, targeted therapies, monoclonal antibodies or
and to modify the standard R-CHOP regimen to improve response, at least for
will come from recognition of the potential refractoriness before beginning treatment
salvage chemotherapy followed with high-dose therapy and autologous transplant in
improve outcome will be presented. Current treatments of these patients associate
separately and prospectively. A review of these different situations and solutions to
'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.

003 ARE WE CHANGING THE NATURAL HISTORY OF FOLLICULAR LYMPHOMA?

For decades many oncologists treating patients with lymphoma have felt that the
overall survival of patients with follicular lymphoma was not significantly impacted by
treatment. 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—mostly in the intermediate grade subset—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
subset of patients for whom watchful waiting is the best initial approach remain
important questions.

key note lectures

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

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
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002 THE ROLE OF THE MICROENVIRONMENT IN LYMPHOMA BIOLOGY

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
alterations 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 (LN). 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.

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