CD20 monoclonal antibody obinutuzumab (GA101) in B-cell lymphoma patients. Blood 2012; **119**: 5126–32.

32. Czuczman MS, Fayad L, Delwail V, ***et al***. Ofatumumab monotherapy in rituximab-refractory follicular lymphoma: results from a multicenter study. Blood 2012; **119**: 3698–704.

VIRUSES AND LYMPHOMA

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Research on oncogenic infectious agents, especially viruses, has helped us to understand the process of malignant transformation of cells because the cellular events in viral-driven transformation mirror, often brilliantly, basic cellular processes that culminate in cancer, even those not associated with viruses. Infectious agents, especially viruses, account for several of the most common malignancies — up to 20% of all cancers. Some of these cancers are endemic, with a high incidence in certain geographic locations, but sporadic/lower incidence in other parts of the world. Lymphomas arise frequently in association with viruses such as Epstein-Barr virus, human herpesvirus 8 (HHV-8), human immunodeficiency virus (HIV), human T-lymphotropic virus-1 (HTLV-1), and hepatitis C virus (HCV). Viruses may contribute to lymphomagenesis either by directly infecting the tumor clone (e.g. EBV, HHV8, HTLV-1), or via indirect mechanisms altering the host immunity (e.g. HIV) or microenvironmental interactions (e.g. HCV).

Gamma-herpesviruses. Two lymphotropic human gamma herpesviruses can cause, or predispose to, lymphoproliferative disorders: Epstein — Barr virus (EBV, formally designated as human herpesvirus 4) and Kaposi sarcoma herpesvirus (KSHV, also called human herpesvirus 8). Individuals with inherited or acquired immunodeficiency have a greatly increased risk of developing a malignancy caused by one of these two viruses. Specific types of EBV- or HHV-8 related lymphomas occur predominantly or almost exclusively in individuals with HIV infection, transplant recipients and children with primary immunodeficiency. Some of these diseases, such as Hodgkin and non-Hodgkin lymphoma resemble those occurring in immunocompetent patients, but the proportion of tumors in which EBV is present is increased. Others, like primary effusion lymphoma and polymorphic post-transplant lymphoproliferative disorders, are rarely seen outside the context of a specific immunodeficient state.

HIV. The clinical features and natural history of HIV-associated lymphomas differ greatly from those observed in the general population. The failure to improve outcomes with treatment intensification indicates the need for the introduction of new therapeutic options. HIV-associated lymphomas still represent a relevant field of clinical research. Standard methodologies for therapy in this patient population have yet to be established. However, rituximab plus chemotherapy should be offered to the majority of patients with HIV infection and diffuse large B-cell lymphoma and the feasibility of intensive aggressive chemotherapy regimens has been successfully tested in HIV-associated Burkitt lymphomas.

HTLV-I. Adult T-cell leukemia-lymphoma (ATLL) is a peripheral T-cell malignancy, closely associated with HTLV-1 infection. Clinically, ATLL is classified into four subtypes: acute, lymphoma, chronic and smoldering type. Although the prognosis of chronic and smoldering-type ATLL is relatively good, that of patients with acute- or lymphoma-type ATLL still remains extremely poor. Zidovudine/IFN-α therapy seems to be promising, although its efficacy has not yet been confirmed in well-designed prospective studies. High-dose chemotherapy with the support of autologous transplantation does not improve outcome. Allogeneic stem cell transplantation is promising and approximately 40% of aggressive ATLL patients are expected to survive long-term, although transplantation-related mortality is as high as 40–50%.

HCV. HCV is well known for its aetiological role in chronic non-A, non-B viral hepatitis, liver cirrhosis and hepatocellular carcinoma; in addition, the virus has also been implicated in a number of extra-hepatic "autoimmune" disease manifestations. A causative association between HCV and non-Hodgkin lymphoma (NHL) was postulated relatively recently and has been the subject of intense investigation, as well as some debate. On the strength of epidemiological data, emerging biological investigations and clinical observations, HCV appears to be involved in the pathogenesis of at least a proportion of patients with NHL. Morphologically, HCV-associated lymphomas represent a variety of histological subtypes including marginal zone lymphoma (splenic, nodal and extranodal), small lymphocytic lymphoma/chronic lymphocytic leukaemia, lymphoplasmacytic lymphoma and diffuse large B-cell lymphoma. Remarkably, some HCV-associated NHL appear to be highly responsive to antiviral therapy, providing some clinical evidence for this relationship, as well as the prospect for novel therapeutic intervention.

Perspectives. Some virus-related lymphomas may be difficult to treat with conventional approaches. Despite recent advancements using cytotoxic, lymphoma-specific, and adoptive therapies, the long-term outcome of patients with y-herpesvirus lymphomas occurring in severely immunocompromised patients and ATLL continues to be poor. Lytic-inducing therapies targeting NF-κB, and viral and tumor cell epigenetic mechanisms afford the advantage of exploiting the intrinsic presence of oncogenic viruses to eradicate infected tumor cells. On these grounds, novel clinical approaches targeting viral latency are currently being investigated.

REFERENCES

1. Carbone A, Gaidano G. Acquired immunodeficiency syndrome-related cancer. A study model for the mechanisms contributing to the genesis of cancer. Eur J Cancer 2001; **37**: 1184–7.

2. Cesarman E. Gammaherpesvirus and lymphoproliferative disorders in immunocompromised patients. Cancer Lett 2011; **305**: 163–74.

3. Gaidano G, Capello D, Carbone A. The molecular basis of acquired immunodeficiency syndrome-related lymphomagenesis. Semin Oncol 2000; **27**: 431–41.

4. Gaidano G, Carbone A. Primary effusion lymphoma: a liquid phase lymphoma of fluid-filled body cavities. Adv Cancer Res 2001; **80**: 115–46.

5. Gantt S, Casper C. Human herpesvirus 8-associated neoplasms: the roles of viral replication and antiviral treatment. Curr Opin Infect Dis 2011; **24**: 295–301.

6. Marcucci F, Mele A. Hepatitis viruses and non-Hodgkin lymphoma: epidemiology, mechanisms of tumorigenesis, and therapeutic opportunities. Blood 2011; **17**: 1792–8.

7. Michieli M, Mazzucato M, Tirelli U, De Paoli P. Stem cell transplantation for lymphoma patients with HIV infection. Cell Transplant 2011; **20**: 351–70.

8. Ramos JC, Lossos IS. Newly emerging therapies targeting viral-related lymphomas. Curr Oncol Rep 2011; **3**: 416–26.

9. Spina M, Gloghini A, Tirelli U, Carbone A. Therapeutic options for HIV-associated lymphomas. Expert Opin Pharmacother. 2010; **11**: 2471–81.

10. Yodoi J, Maeda M. Discovery of ATL: an odyssey in restrospect. Int J Hematol 2011; **94**: 423–8.

LEUKEMIC PHASE OF B-LINEAGE NHL

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B-cell non-Hodgkin lymphomas (NHL) mostly present as disseminated diseases involving lymph nodes, spleen and liver and often the bone marrow (BM). Tumor cells can also be found in the blood (leukemic disease), especially in the indolent lymphomas. High white blood cell counts and a differential demonstrating a lymphocytosis in the blood require immunophenotyping for characterization of the leukemic cells. Molecular/cytogenetic analyses may also have a role in the diagnostic classification of the disease. Besides the specific diagnosis, the clinical evaluation of the patient and prognostic markers are of most importance for selecting the best type of therapy.

Follicular lymphoma (FL) is the indolent lymphoma with the highest incidence. Most patients present with advanced stage disease with BM involvement in 40–70% of the cases, and few are leukemic at the time of diagnosis. By high-resolution analysis circulating FL cells may be detected in more patients. Leukemic patients mostly have concomitant lymph node involvement and high tumor burden. A pure FL-cell leukemia with $CD20^+CD10^+CD5^-$ clonal cells has also been described, mostly associated with an indolent clinical outcome. FL carry a t(14;18)(q32;q21) translocation in more than 90% of cases, juxtaposing the immunoglobulin heavy chain (IGH) 3' Regulatory Regions (IgH-3'RR) to the *BCL2* gene, resulting in overexpression of the Bcl2 anti-apoptotic protein. FL cells are also dependent on signals from the microenvironment to survive and proliferate. Several groups, including ours, have reported that immune cells in the lymphoma microenvironment and in blood influence prognosis. In patients treated before the introduction of rituximab, we have found that a high number of PD-1^+, $FOXP3^+$ and $CD8^+$ T-cell subsets in the tumor microenvironment predict superior outcome, while $CD4^+$ follicular helper T cells and $CD68^+$ macrophages are associated with an inferior outcome. The introduction of the anti-CD20 antibody rituximab has improved the prognosis for FL patients. The efficacy of this drug is excellent also as monotherapy especially in patients with high numbers of $CD8^+$ T-cells in the lymph nodes as well as in the blood.

***Mantle cell lymphoma (MCL)*:** MCL cells carries the t(11:14) translocation resulting in enhanced cyclin D1 expression and cyclin D1-dependent kinase activity, promoting cell cycle progression. Immunological markers show a typical phenotype ($CD20^+CD5^+CD23^-$), but also atypical phenotypes ($CD20^+CD5^-CD23^-$ or $CD20^+CD5^+CD23^+$) in some cases. Most MCL patients have an unfavorable prognosis and intensive treatment strategies are required. However, in around 10% of the patients the disease shows an indolent clinical course with often a non-nodal, leukemic disease. In one study the clinicopathologic features, gene expression and genomic profiles were compared in patients with indolent (iMCL) and in those with conventional disease (cMCL). iMCL and cMCL shared a common gene expression profile that differed from other leukemic lymphoid neoplasms and a signature of 13 genes was underexpressed in iMCL, among these *SOX11*. The *SOX11*-negative tumors exhibited more frequent non-nodal presentation and better survival compared with *SOX11*-positive MCL. Recently, our group found that *SOX11*-negative MCL had a higher frequency of lymphocytosis, but also elevated LDH and p53 positivity. Moreover, *SOX11*- negative cases had a shorter overall survival than *SOX11*-positive cases. Due to the conflicting results, the conclusion is that *SOX11* cannot be used for predicting an indolent disease course. In another study, deletions at 17p13 *(TP53)* and 13q14 were frequent in leukemic MCL and involved the majority of the leukemic clone. Cases with *TP53* deletion were more likely to have splenomegaly and marked leucocytosis ($> 30 \times 10^9$/L), and were less likely to have lymphadenopathy than those without the deletion. Other distinctive biological features in non-nodal leukemic MCL are mutated IGHV and a transcriptional profile lacking tumor invasion properties, which might contribute to the absence of nodal involvement. In conclusion, MCL patients with leukemic disease but without clinical symptoms might be managed conservatively with a "wait and watch" policy, while blastoid morphology, high proliferation and *TP53* aberrations are markers of aggressive disease, which will require intensive immunochemotherapy.

Marginal zone lymphoma (MZL): There are three clinicopathological entities of MZL, including extranodal, mucosa-associated lymphoid tissue (MALT) lymphoma, nodal (NMZL), and splenic (SMZL) type. Leukemic presentation is more common in SMZL. The leukemic