

Hodgkin's Lymphoma: New Insights in an Old Disease

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Volker Diehl, Andreas Engert, and Daniel Re

World Health Organization and Beyond: New Aspects in the Pathology of an Old Disease

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Michael Hummel

Hodgkin's lymphoma is a highly enigmatic lymphoma disease that still covers most of its secrets up to now. Much effort has been made to successfully wrest at least some of the pathogenetic particularities. The current diagnostic criteria are well established allowing hematopathologists to make a clear-cut distinction from other lymphomas in almost all cases. Although classic Hodgkin's lymphoma is curable in the vast majority of cases by treatment with highly aggressive drugs with or without radiotherapy, further molecular studies may lead to the identification of therapeutic targets that enable a more tailored treatment with fewer side effects.

The Pathogenesis of Classical Hodgkin's Lymphoma: A Model for B-Cell Plasticity

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Stephan Mathas

It has been shown that differentiated lymphoid cells can display a broad developmental potential and might even differentiate into other cell types. Recent data implicate such processes in the pathogenesis of classical Hodgkin's lymphoma (HL). In the malignant, B cell-derived Hodgkin's and Reed-Sternberg (HRS) cells of HL the expression of B cell-specific genes is lost, and B lineage-inappropriate genes are up-regulated. Experimental evidence has been presented in recent years that functional disruption of the B lineage-specific transcription factor program contributes to this process. HRS cells might be reprogrammed into cells resembling undifferentiated progenitor cells, which might offer an explanation for the unique HL phenotype and demonstrate a high degree of plasticity of human lymphoid cells.

**The Potential Role of the Innate Immunity
in the Pathogenesis of Hodgkin's Lymphoma** **805**Gunilla Enblad, Daniel Molin, Ingrid Glimelius, Marie Fischer,
and Gunnar Nilsson

The innate immune system is our first line of defense against danger signals but in Hodgkin's lymphoma the role seems opposite, favoring malignant development. In this article we describe interactions between Hodgkin's and Reed-Sternberg cells and the cells of the innate immune system: eosinophils, mast cells, neutrophils, and macrophages. These cells clearly contribute to the pathogenesis of this disease and to the prognosis. Cytokines and chemokines released from the activated immune cells probably promote tumor cell growth and survival along with angiogenesis. Mast cells and eosinophils seem also to contribute to the fibrosis that is so characteristic for nodular sclerosis.

**New Aspects in Descriptive, Etiologic,
and Molecular Epidemiology of Hodgkin's Lymphoma** **825**

Ola Landgren and Neil E. Caporaso

Epstein-Barr virus (EBV) has remained the main candidate suggested as the infection causing Hodgkin's lymphoma for several years. However, EBV genome has been found only within the tumor in about 20%–40% of Hodgkin's lymphoma cases with a prior diagnosis of infectious mononucleosis. Recently, autoimmune and related conditions have drawn attention to a potential role for immune-related and inflammatory conditions in the etiology and pathogenesis of the malignancy. Evidence from multiple affected families from case series, a twin study, a case-control study, and population-based registry studies implicate a role for genetic factors. Simultaneously, data from Eastern Asia and among Chinese immigrants in North America indicate increasing incidence trends for Hodgkin's lymphoma being associated with westernization. These results emphasize an interaction between environmental and genetic risk factors in Hodgkin's lymphoma.

**The International Harmonization Project
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Bruce D. Cheson

Clinical trials are critical to the development of newer and more effective treatments. Standardized response criteria are essential to assess and compare the activity of various therapies within and among studies and to facilitate the evaluation of new treatments by regulatory agencies. The International Harmonization Project developed revised guidelines with the goal of improved comparability among studies, leading to accelerated new agent development resulting in the rapid availability of improved therapies for patients who have lymphoma. Modifications of these recommendations are expected as new information and improved technologies become available.

Is [¹⁸F]fluorodeoxyglucose Positron Emission Tomography the Ultimate Tool for Response and Prognosis Assessment? **855**
Lieselot Brepoels and Sigrid Stroobants

[¹⁸F]fluorodeoxyglucose positron emission tomography (FDG-PET) is currently the most accurate and reliable tool for the assessment of response in Hodgkin's lymphoma (HL). FDG-PET is superior to conventional imaging techniques for detection of residual disease at the end of treatment, especially in the presence of a residual mass, a frequent finding in HL. FDG-PET response assessment has also a high predictive value early after the initiation of therapy. However, whether risk-adapted treatment strategies based on FDG-PET may also improve patient outcome remains to be proved.

New Strategies for the Treatment of Early Stages of Hodgkin's Lymphoma **871**
David A. Macdonald and Joseph M. Connors

The treatment of early or limited-stage Hodgkin's lymphoma continues to evolve. With the likelihood of cure of the lymphoma approaching 95% it has become increasingly necessary to balance improved effectiveness of treatment with minimization of troublesome late toxicity. Carefully crafted treatment strategies based on optimal combinations of brief chemotherapy and involved-field radiation or even reliance on brief chemotherapy alone for carefully selected patients have emerged as the most attractive approaches to achieve this important balance.

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Lena Specht and John Raemaekers

The outcome of patients who have early unfavorable or intermediate-stage Hodgkin's lymphoma has greatly improved. The increasing efficacy of chemotherapy and late toxic effects of wide-field radiotherapy justify the careful testing of the new involved-node radiotherapy principle in the combined-modality approach. For the purpose of tailoring treatment to the individual patient we need more accurate measures, preferably predictive factors that may tell us how the individual patient should be treated. The result of an early positron emission tomography scan with fluorodeoxyglucose may well become the major new treatment-related guidance for an individually tailored treatment approach.

New Strategies for the Treatment of Advanced-Stage Hodgkin's Lymphoma **897**
Volker Diehl, Andreas Engert, and Daniel Re

In 2007, patients who have Hodgkin's lymphoma, even in advanced stages, have a better than 85% chance of being cured of their disease

if adequate therapy is given at the outset. Most ongoing or planned international studies tailor therapy according to the needs of the individual patient, also accounting for anatomic stage, tumor burden, age, gender, and biologic host factors that affect prognosis. With this approach it might be possible to use less aggressive treatment regimens for the lower-risk groups and limit the use of the more aggressive dose- and time-intensified/dense regimens for the higher-risk groups. With this individualized approach it might be possible to yield higher cure rates and simultaneously reduce the risk for late complications and mortality.

Hodgkin's Lymphoma: The Role of Radiation in the Modern Combined Strategies of Treatment

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Richard T. Hoppe

A history of the treatment of Hodgkin's disease with radiation therapy and chemotherapy is presented. Studies are reviewed examining treatment for favorable and unfavorable presentation of stage I–II disease, stage III–IV disease, and relapsed disease. In this era of combined-modality therapy we have reached the point of near-total conquest of Hodgkin's lymphoma, but challenges remain. Directions for future research are discussed.

Relapsed and Refractory Hodgkin's Lymphoma: New Avenues?

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George P. Canellos

Relapse or progression following therapy for Hodgkin's lymphoma occurs in 10% to 60% of patients depending on initial clinical stage. Patterns of failure in advanced disease determine prognosis of salvage therapy. Progression or early relapse after less than 12 months requires intensive salvage therapy. Only late, isolated, asymptomatic relapse, which occurs in less than 25% of those relapsing from systemic therapy, can be treated with conventional-dose chemotherapy with or without radiation. Overall about 40% to 50% of relapses from advanced disease can be salvaged with higher percentages for patients relapsing from early stage disease.

Autologous and Allogeneic Stem Cell Transplantation in Hodgkin's Lymphoma

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Anna Sureda

Newly diagnosed patients who have advanced-stage Hodgkin's lymphoma have an excellent prognosis because most of them can be cured with initial treatment. In contrast, the prognosis for patients relapsing after first-line therapy with either combination chemotherapy or chemotherapy followed by radiotherapy remains poor in many cases. In most

of these cases, high-dose chemotherapy and autologous stem cell transplantation (ASCT) is currently considered to be the treatment of choice. However, results of ASCT in primary refractory patients are poor and new therapeutic alternatives should be sought for these patients. Allogeneic stem cell transplantation has been used increasingly in relapsed or refractory Hodgkin's lymphoma patients, with the introduction of reduced-intensity conditioning protocols.

Are We Improving the Long-Term Burden of Hodgkin's Lymphoma Patients with Modern Treatment?

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Berthe M.P. Aleman and Flora E. van Leeuwen

The cure rate of patients who have Hodgkin's lymphoma (HL) amounts to 80% or more because of risk-adapted treatment using modern chemotherapy and radiotherapy schedules. In this article we describe important late effects after treatment of HL and how we expect the long-term burden of patients who have HL to change applying modern treatments. Because treatment always has side effects to some extent, awareness of possible late effects after treatment remains important for patients and treating physicians.

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