

thrombosis and bleeding, progression to myelofibrosis and transformation to acute leukemia. Myelosuppressive therapy, preferentially with hydroxyurea, can reduce the rate of vascular complications, but there is some concern about an increased rate of leukemic transformation with this agent. Therefore, management of these disorders poses a significant challenge, and a risk-oriented therapeutic approach should be followed to avoid inappropriate exposure to cytotoxic drugs on one side or suboptimal treatment on the other. Established risk factors for cardiovascular events are represented by older age and previous thrombosis, while impact of novel biological factors, including leukocytosis and JAK2V617F mutational status and/or mutational burden, is under active investigation. Low-risk PV patients should be managed only with phlebotomy and aspirin, while high-risk patients should also receive cytotoxic therapy. Regarding the management of ET, there is no clear indication for intervention in low-risk patients, while high-risk patients should be managed with chemotherapy. Other therapeutic options, such as interferon alpha or anagrelide, may find place in selected patients including those who are resistant/intolerant to hydroxyurea.

Primary Myelofibrosis PMF is a clonal disorder arising from an early stem cell and the stromal bone marrow reaction is due to fibrogenic and angiogenic cytokines derived from clonal megakaryocytes. Managing patients with myelofibrosis (MF) is a difficult task. Patients suffer from a variable, but severe range of disease manifestations including massive splenomegaly, cytopenias, significant constitutional symptoms, possible transformation to blast phase and premature death. Clinical trials with new nonspecific-targeted therapies have confirmed that their use in PMF is of modest clinical activity. Cure is achievable through allogeneic stem cell transplantation.

There is a great expectation for novel drugs targeting the constitutively active JAK2/STAT pathway. Over a dozen JAK2 inhibitors are in development, with some leading compounds showing promising early results particularly for control of disease associated splenomegaly and symptoms. Parallel trials with immunomodulatory therapy for MF associated anemia and stromal manifestations of the disease are continuing. The future may well see the approval of a range of agents for MPN patients, with differing mechanisms of action, efficacy and toxicity profiles.

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Lymphomas and myeloma

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New biological determinants in lymphoma

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Prognostication for lymphoma patients has always been a challenge, given the heterogeneity of histology, clinical presentation, and underlying biological mechanisms driving the aggressiveness of the disease. They help to provide information towards the patient, to choose the optimal therapeutic approach, to compare clinical trials, and may also lead to identify patient's groups eligible for targeted therapies. From immunohistochemical markers to gene expression profile, a number of approaches have been developed in the last 20 years, providing new tools and indexes. Most of these biomarkers were rationally based on our improved understanding of lymphoid differentiation and malignant lymphoma biology. Few have however spread in clinical practice for multiple reasons, including their accessibility or their cost, their reproducibility and robustness, but also their lack of validation in large cohorts. In order to gain a better knowledge of the power of IHC biomarkers to help prognosticate diffuse large B-cell (DLBCL) lymphoma patients, Lunenburg Lymphoma Biomarker Consortium (LLBC) evaluated a large international patients cohort in order to investigate a new clinicobiological prognostic index. Clinical data and pathological samples were retrieved from 12 clinical studies from Europe and North-America, with patients treated before (e-CHOP group) or after the rituximab era. Using tissue microarrays from 1514 of these 2451 patients, IHC for BCL2, BCL6, CD5, CD10, MUM1, Ki67 and HLA-DR was performed and scored according to previously validated protocols. Optimal cut points were then determined and the prognostic value for overall survival of individual markers, their interrelation and interaction with the International Prognostic Index (IPI) were assessed to investigate a combined index.

This presentation will include the description of objective cut-points identified, newly recognized correlations between

biomarkers and IPI, and indices which allow subtle refinements for identification of only low-risk patients. These data underline the need for critical biomarker validation in DLBCL.

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Open questions in the treatment of follicular lymphoma

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The introduction of monoclonal antibodies (in particular rituximab) in the treatment algorithm of follicular lymphoma has significantly improved the median survival of this disease. Nevertheless, with the exception of a few special cases, it remains an incurable disease. A number of questions remain open and we are going to discuss three of them: Is watch and wait still an option? Is R-CHOP the standard first-line treatment? What is the role of autologous and allogeneic transplantation?

The attitude of watching and waiting is regularly challenged because of concerns that delaying treatment could cause irreversible organ damage, permit the general condition of the patient to reduce, allow the appearance of chemotherapy resistant clones or transformation to high-grade lymphoma. Studies and experience confirm that, due to the usually slow progression of the disease, if a strict policy of regular follow-up visits is in place, organ damage and performance status reductions are readily recognized and dealt with. Studies also show that resistance to chemotherapy is not dependent on stage and finally transformation to high-grade is independent from the timing of first-line treatment. The 4 randomised studies performed in the last 2 decades confirmed that watch and wait does not confer a worse survival compared to immediate initial treatment.

The very good partial and complete response rates and response duration seen with aggressive first-line treatment, as CHOP combined with rituximab, has prompted some cooperative groups and centers to elect this regimen as a standard first-line. Nevertheless, many studies have shown in the past that increased response rate and duration do not translate into prolonged survival. This is still true today and the comparison of many studies with different kinds of protocols, ranging from single agent chemo- or immunotherapy to very complex and aggressive combination treatments all show in the long term (as 7 years follow-up) similar progression free survival rates. In addition, the recent demonstration that the combination of rituximab and single agent bendamustine is better tolerated and as active as R-CHOP will further question the primacy of R-CHOP as first-line treatment. Several randomised trials are still ongoing to clarify which first-line treatment, if any, is optimal for follicular lymphoma.

High-dose chemotherapy with autologous stem cell transplantation proved to be a good salvage treatment for patients in first or second relapse. According to one small randomised and a few historical studies, this strategy could prolong survival compared to standard salvage chemo-immunotherapy. Nevertheless, in first-line, four randomised studies show no advantage for this strategy. It is probable that the secondary MDS/AML and the acute toxicities could jeopardise the minimal survival advantage. On the other hand allogeneic transplantation is probably the sole modality with curative potential in this disease. Nevertheless, it is

bound to very important acute toxicity, translating in almost 50% early deaths in the first year after transplantation. Because of this, despite of the curative potential, this modality is kept for patients with early aggressive relapse, who are young and fit enough to tolerate the treatment.

In conclusion the treatment algorithm for first-line follicular lymphoma should consider prognostic factors, symptoms and patient subjective priority to choose among watch and wait, intensive treatment or a milder treatment with single agents.

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Diffuse large B-cell lymphoma

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Treatment of diffuse large B-cell lymphomas (DLBCL) in the years 80-90's was characterized by various attempts to improve the results obtained with the classical CHOP regimen, including introduction of alternate drugs with CHOP, development of dose dense or intense regimens, or consolidation with high dose therapy (HDT). Those strategies yielded to some progress, usually restricted to some patients' subgroups, but were not adapted worldwide. The introduction of the anti-CD20 monoclonal antibody rituximab 10 years ago represented a new step forward, which significantly improved the survival of DLBCL patients. Although the benefit of rituximab use may differ in certain patients' subgroups, this lead to commonly administer immunochemotherapy in all DLBCL patients. This new R-CHOP standard may however challenge some of the previous findings from earlier trials and therefore their underlying concepts. Recent data regarding dose dense or dense intense chemotherapy combined with rituximab will be discussed. The recent introduction of