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 primate 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 fist 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 form 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

new imaging techniques, essentially represented by 18-FDG PET-scan, also seems to modify our practice in DLBCL treatment. Other approaches are based on the introduction of new therapeutic compounds, targeting the tumor cells itself or its micro-environment: anti-angiogenic compounds, proteasome or mTOR inhibitors, IMIDs. Some of these drugs may benefit to selected patients subgroups, characterized by particular biological features. Current standards, options and investigational therapeutic approaches in various subgroups of DLBLC patients will also be discussed.

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Recent progress in the treatment for T-cell malignancies

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New therapeutic approaches and the incorporation of novel agents into these therapeutic regimens are necessary to improve the outcome for peripheral T-cell lymphoma (PTCL) patients.

Nucleoside analogs: Nucleoside analogs are chemotherapeutic agents that primarily inhibit DNA replication and repair. There are three subgroups of nucleoside analogs: pyrimidine nucleoside analogs, purine nucleoside analogs, and the metabolic enzyme inhibitors. Gemcitabine is the most effective pyrimidine nucleoside analog in PTCL. It has been active both as a single agent and in combination with alemtuzumab and bortezomib. The purine nucleoside analogs include cladribine, fludarabine, clofarabine, and nelarabine. Both cladribine and fludarabine have shown efficacy in PTCL, and clofarabine and nelarabine are currently in several clinical trials in T-cell lymphoma.

Monoclonal antibodies: The addition of the anti-CD20 monoclonal antibody (MAb) rituximab to chemotherapy regimens like CHOP has significantly improved treatment outcomes in B-cell lymphoma. As such, several monoclonal antibodies are currently being tested in PTCL, including alemtuzumab, iratumumab, siplizumab, and zanolimumab.

Conjugates: Denileukin diftitox is an antineoplastic agent that combines interleukin-2 with diphtheria toxin, and it has been approved by the US Food and Drug Administration (FDA) for use in cutaneous T-cell lymphomas (CTCL). In PTCL patients, the combination of denileukin diftitox and CHOP produced enhanced response rates (ORR of 86.5%) when compared to historical data using CHOP alone.

Proteasome inhibitors: Bortezomib, a proteasome inhibitor, has been well tolerated and active as a single agent in relapsed or refractory CTCL patients. It has also been used with positive results in combinations with gemcitabine ± doxorubicin, and recent evidence shows that bortezomib may synergize with pralatrexate in T-cell lymphoma (see folate analog section below).

Histone deacetylase inhibitors: Histone deacetylase (HDAC) inhibitors are potent inducers of histone acetylation, which results in the expression of tumor suppressor genes that had been previously silenced by deacetylation. This gene expression leads to cell cycle arrest and apoptosis. There are a number of HDAC inhibitors being used or studied in T-cell lymphoma, including vorinostat, romidepsin (also known as depsipeptide), panobinostat, and belinostat. Vorinostat and romidepsin have shown single-agent activity in CTCL, and vorinostat was approved by the FDA in 2006 for the treatment of cutaneous T-cell lymphoma (CTCL). There is limited data on the activity of HDAC inhibitors in PTCL, and further study is needed for HDAC inhibitors, both as single agents and in combination with other types of agents, such as retinoids, antiangiogenic agents, proteasome inhibitors, chemotherapeutic agents, and demethylating agents.

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Mantle cell lymphoma: Current standards and new approaches

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Mantle cell lymphoma (MCL) is a unique subtype of B-cell non-Hodgkin's lymphomas characterized by the chromosomal translocation t(11;14)(q13;q32) and nuclear cyclin D1 overexpression in the vast majority of cases.

Most patients present with advanced stage disease, often with extranodal dissemination, and pursue an aggressive clinical course in the majority of cases [1]. With the exception of allogeneic hematopoietic stem cell transplantation, current treatment approaches are non-curative and the corresponding survival curves are characterized by a delayed, but continuous decline and a median survival of 4–6 years [2,3]. However, a subset of 15 % long-term survivors have been identified with a rather indolent clinical course even after conventional treatment strategies only [4].

Recently, a prognostic score has been established implementing age and performance status of the patient, LDH and leukocyte count [5]. Moreover, the strong prognostic impact of minimal response has been increasingly recognized [6].

At least concerning initial response rates, improvement has been achieved by the successful introduction of monoclonal antibodies with a CHOP-like or other conventional chemotherapies [7,8]. In younger patients, dose-intensified approaches including autologous stem cell transplantation (ASCT) strategies has further improved progression-free survival rates [3,9,10].

Emerging strategies including proteasome inhibitors [11], IMIDs [12], mTOR inhibitors [13] and others are based on the dysregulated control of cell cycle machinery and impaired apoptotic pathways. Monotherapy of these compounds achieve efficacy comparable to conventional chemotherapy in relapsed MCL, and combination strategies are currently being investigated in numerous trials, however their introduction into clinical practice and current treatment algorithms remains a challenge [14].

Full protocol versions of the *European MCL Network* are available under: www.european-mcl.net.

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