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.

14
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.

15
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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Autologous transplantation in lymphoma: Has rituximab changed the scenario?

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More than 20 years ago the use of autologous hematopoietic stem cell transplantation was shown to be able to cure patients with recurrent aggressive B-cell lymphomas. Patients were more likely to be cured if they had relapsed from a chemotherapy induced complete remission and continued to respond, at least partially, to further chemotherapy regimens. The use of autologous transplantation as part of the primary therapy for patients with poor risk characteristics has remained controversial despite multiple clinical trials. More recently, autologous transplantation has been shown to yield durable responses in ~40% of patients with follicular lymphoma in second remission and has been reported to improve the treatment outcome in patients with mantle cell lymphoma when included in the initial treatment regimen. When rituximab was first introduced into the transplant process, it was reported to yield a higher relapse-free survival when given before transplant and seemed to provide a method of "in vivo" purging when given before stem cell collection. The anticipated side effects of infusion reaction and rare cardiac and pulmonary toxicities are seen when the drug is incorporated into the transplant process. There has also been an unusual late neutropenia seen in patients who receive rituximab before or after autologous transplantation. However, the most important recent finding was somewhat unexpected. Rituximab improves the cure rate of patients with diffuse large B-cell lymphoma by approximately 15%. Thus, fewer patients will be eligible for salvage transplants. When salvage transplants are performed on patients who were initially treated with a rituximab containing combination chemotherapy regimen, the event-free survival seems lower than in patients who never received rituximab. For example, in a Spanish study the three-year progression-free survival dropped from 57% to 17% when comparing patients who never received rituximab with those who had initial treatment including rituximab. The CORAL study found a three-year event-free survival decrease of 47% to 21%. This might be related to rituximab resistance related to previous exposure, or a more resistant group of patients being transplanted after failing an initial rituximab containing regimen. However, it still may be that auto transplant is the superior therapy for patients with relapsed, chemotherapy sensitivity aggressive lymphoma. The "overall" cure rate for these patients may not have changed, but fewer will be salvaged with transplantation.

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Fluorodeoxyglucose (FDG) positron emission tomography (PET) in Lymphoma

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Fluorodeoxyglucose positron emission tomography (FDG-PET) is being increasingly incorporated into the management of lymphoma, due to its unique ability to reflect the metabolic activity of malignant cells in vivo.
FDG-PET has proved to have a higher sensitivity than CT in the staging of Hodgkin Lymphoma (HL) and Diffuse Large B-cell Lymphoma (DLBCL), identifying both nodal and extranodal sites of disease not detected by conventional imaging. It has further been shown to discriminate between 'active' lymphoma and scar tissue following therapy leading to a re-definition of the response criteria, eliminating the category of 'CRu' [1,2].
There is an increasing body of evidence suggesting that it may be possible to individualise therapy on the basis of functional imaging after the first two cycles of treatment [3,4]; randomised clinical trials are testing this hypothesis.
During the course of the next decade the full potential of PET scanning will become apparent. Meanwhile it remains to be established which method of interpreting the result is optimal and whether its use extends beyond HL and DLBCL.

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