Diagnosis and actual therapy strategies in peripheral T-cell lymphomas: summary of an international meeting

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Received 13 May 2003; revised 31 July 2003; accepted 13 August 2003

Key words: histopathology, immunology, molecular biology and genetics, peripheral T-cell lymphoma, treatment

Introduction

Peripheral T-cell lymphomas (PTCL) according to the REAL classification (mature T-cell lymphomas of the WHO classification) comprise no more than 10% of all non-Hodgkin’s lymphomas in the Western hemisphere [1]. Until now, uncertainties regarding many features of these rather heterogeneous diseases have prevented progress in developing effective therapies. PTCL has often been assessed as part of clinical studies focusing on the more common B-cell lymphomas and, consequently, our understanding of how to treat this group of lymphomas remains less clear than for B-cell lymphomas.

With the exception of a few subgroups, the prognosis of PTCL is poor, partly due to a limited understanding of their pathophysiological features. There is considerable variability in clinical presentation, which may greatly prolong the time taken to reach an accurate diagnosis in an individual patient. Additionally, treatment standards in PTCL have not yet been established [2].

Challenged by this variety of problems, the authors of this report organized a workshop in Schlangenbad, Germany, in late September 2002. Investigators from different backgrounds, including biology, pathology, molecular biology and genetics, dermatology, and hematology/oncology, presented and discussed updated knowledge and their own data on a variety of topics relating to PTCL, within sessions on immunology and histological classification; cytogenetics and molecular genetics; treatment of primary cutaneous and disseminated T-cell lymphomas; antibody treatment of T-cell malignancies; and recently published, current studies in PTCL. The aim of the workshop was to begin coordinating activities in experimental and clinical research in this group of lymphomas. This meeting report summarizes the main statements and conclusions of each session.

Immunology and histological classification

The workshop opened with a review of the biology of T and natural killer (NK) cells, by D. Kabelitz (Kiel). T cells bearing the αβ T-cell receptor (TCR) represent ~95% of peripheral T cells, and recognize processed antigen presented as peptides either by major histocompatibility complex (MHC) class I molecules to CD8+ or by class II molecules to CD4+ cells. In contrast, most TCR γδ T cells recognize low molecular weight phosphorylated metabolites derived from the bacterial biosynthesis pathway, and are thus important for immune defense against bacterial infections [3]. Besides the TCR level, there is considerable functional heterogeneity among T cells. For example, CD4+ cells can be functionally divided into T helper 1 and 2, according to their spectrum of cytokine expression. More recently, regulatory T cells mediating suppressive effects have been described, which are defined by the expression of the interleukin (IL)-2 receptor α chain and IL-10, as well as transforming growth factor (TGF)-β [4]. NK cells do not express TCRs on their surface, but do express a group of C-type lectin and immunoglobulin-like receptors, the so-called ‘killer’ inhibitory receptors (KIR), which bind to human leukocyte antigen (HLA) class I molecules (e.g. HLA-C, HLA-E) and mediate inhibiting or activating signals. The discovery of these MHC class I receptors has considerably enhanced our understanding of the biology of NK cells. Up to seven different KIR can be expressed on a single NK cell. Preliminary new data indicate that accurate typing of HLA and KIR may have an important role in transplantation, especially in haploidentical settings [5].

M.-L. Hansmann (Frankfurt) presented insights into the molecular pathology of angioimmunoblastic T-cell lymphoma (AILD), a disease that is currently defined as a PTCL, although certain cases lack any clonality of CD4+ and CD8+ populations. In AILD with clonal expansion of CD4+ cells, Hansmann and co-workers [6] detected overexpression of certain TCR Vβ segments, possibly suggesting that a superantigen trigger causes some cases of the disease [7]. Moreover, Hansmann presented new data explaining the clonal expansion of B cells in AILD, resulting in...
so-called ‘forbidden B cells’. Single-cell studies in B cells, which are frequently infected with the Epstein–Barr virus (EBV) in AILD, revealed oligoclonal or sometimes large clonal expansions of these cells. Most EBV+ cells carried mutated Ig rearrangements, indicating that EBV resided mostly in memory or germinal center B cells. Ongoing somatic hypermutations were frequently observed, often resulting in mutations disrupting Ig gene expression. As, physiologically, B cells with such mutations undergo apoptosis, the surviving B cells with destructive mutations, which were also found to be present in EBV– cells, were named ‘forbidden B cells’ [7, 8]. Hence, the group concluded that the micro-environment in AILD is likely to promote survival and clonal expansion of this new cell population.

Definitions of neoplastic populations and prognostic factors in nodal T-cell lymphomas, based on our own experience and that of the Non-Hodgkin’s Lymphoma Classification Project, were described by Th. Rüdiger (Würzburg). Clonality was analyzed by studies of the TCR Vβ family using immunophenotyping and PCR. In AILD, survival was independent of mono- or polyclonality of T cells. However, in cases of high-grade AILD, defined by the presence of clear cell clusters or high numbers of large, atypical blasts, T-cell clonality was significantly higher than in low-grade disease. Confirming the results of others, and in agreement with the previous presentation, clonal populations were found significantly less frequently in AILD than in PTCL not otherwise specified (PTCL-NOS). In PTCL-NOS, survival was significantly associated with several risk factors, including grade, age, stage, performance status, lactate dehydrogenase (LDH) level and response to primary therapy, whereas in AILD, only younger age and remission in response to therapy were favorable prognostic factors [7]. From the data presented, Rüdiger suggested that PTCL-NOS should be analyzed separately from AILD with regard to prognostic factors. Furthermore, he pointed out that analysis of clonality by TCR Vβ gene expression studies can be utilized to detect minimal residual disease and relapse.

C. Sander (Munich) reviewed the current classification systems in cutaneous T-cell lymphomas (CTCL), which present as a heterogeneous group of PTCL showing variations in presentation, histology, immunophenotype and prognosis. At presentation, cutaneous lymphomas may be primary or may involve the skin as a secondary site of involvement. Their natural history is often more indolent than in nodal lymphomas and, for this reason, they often require different therapeutic approaches. A classification scheme should recognize those lymphomas that are unique to the skin, as well as those arising in other sites. In Sander’s opinion, an organ-specific classification system hinders the possibility of consensus among different medical specialties. For this reason he favors the comprehensive approach offered by the World Health Organization (WHO) classification of hematopoietic and lymphoid malignancies, which proposes that lymphomas should be viewed as a list of individual diseases, and that each disease can be defined by a constellation of morphological, biological and clinical features [9].

Cytogenetics and molecular genetics

The session on cytogenetics and molecular genetics began with a review by M. Bentz (Ulm) of the history and technical development of currently available techniques. Furthermore, he introduced a genomic profiling technique in the form of a lymphoma oncogene chip, which he has developed in collaboration with P. Lichter (Heidelberg) [10]. This comprises probes from 645 clones, of which 372 cover potentially critical genomic regions (e.g. 12q13–12q15) and regions where tumor suppressor genes are located. All the methods described are being applied or are potentially applicable in PTCL. Questions that remain to be addressed include the significance of recurrent aberrations and their implications for prognosis. Furthermore, molecular mechanisms of pathogenesis may be more narrowly defined by analysis of genomic gains or losses using comparative genomic hybridization (CGH) and matrix-CGH. Bentz described, as an example, a model for the development of T-cell prolymphocytic leukemia (T-PLL): loss or biallelic mutations of the ataxia-telangiectasia mutated (ATM) gene—a frequent occurrence in T-PLL—may be involved in the initiation of the malignant process [11]. A subsequent gain or activation of the T-cell lymphoma-1 (TCL-1) gene may lead to proliferation, and further modifications to the aggressive character of the disease.

A review of the cytogenetic and molecular genetic events in PTCL, including our own results [presented by R. Siebert (Kiel)], shows that, with a few exceptions, only scarce and inconsistent data exist on chromosomal aberrations in subtypes of PTCL. As already reported by Bentz, in T-PLL the inv(14)(q11;q32)—or, less frequently, t(14;14)(q11;q32)—can lead to activation of TCL-1, and deletions in 11q22–11q23 affect the ATM gene [11]. The role of other recurrent karyotypes in T-PLL, such as inv(8q)/t(8:8), del(13q14), del(12p13), del(6q) and dup(6p), is unknown [12]. In hepatosplenic T-cell lymphoma, the characteristic aberrations are i(7q) and trisomy 8, but the functional consequences of these changes have yet to be determined [13]. Another well-characterized aberration is t(2;5)(p23;q35) in anaplastic large cell lymphoma (ALCL), which fuses the anaplastic lymphoma kinase (ALK) gene to nucleophosmin (NPM) [14]. Recurrent cytogenetic findings in other PTCL are gains in chromosomes X, 1q, 3, 6p, 7q, 8q, 11q and 17q, and losses in X, 1p, 6q, 9p, 10q, 11q, 13q and 17p. A striking feature in certain PTCL, particularly in angioimmunoblastic lymphoma, is the presence of unrelated clones, a marker denoting the genomic instability that may contribute to the pathogenetic events in these cases.

A. Zettl (Würzburg) presented data on the use of CGH in enteropathy-type T-cell lymphoma and PTCL-NOS. While chromosomal gains at chromosome 9q were found to characterize enteropathy-type T-cell lymphoma [15], gains and losses were more complex in 44 patients with PTCL-NOS. Frequent gains were found at chromosomes 7q (36%) and 9q (18%), and losses at chromosomes 6q (41%), 13q (39%), 5q (27%), 9p (27%), 10q (27%) and 12q (25%). As changes at chromosomes 6q, 13q, 9p and 7q have been described in other PTCL, and losses of 5q and 12q were found more exclusively in PTCL-NOS, Zettl concluded that these regions may represent areas encompassing genes responsible for the development or progression of PTCL-NOS.
Some candidate genes from these loci are now being evaluated for functional properties.

In conclusion, the aims of cytogentic and molecular genetics analysis in PTCL should be to characterize subtypes and prognostic features, and also to clarify the basis of pathophysiological events.

**Treatment of primary cutaneous and disseminated T-cell lymphomas**

C. Sander (Munich) presented an overview on prognosis and current treatment approaches in primary cutaneous lymphomas. He emphasized the heterogeneity of these diseases, in terms of histology, immunophenotype and prognosis, and pointed out that primary cutaneous lymphomas are, in many instances, distinct from morphologically similar lymphomas arising in lymph nodes [16], and that their natural history is more commonly indolent. For example, in the case of cutaneous lymphoma with a favorable prognosis, such as mycosis fungoides, only 15% to 20% of patients die of lymphoma-related complications. Even patients with clinical stage IA may have a normal life expectancy. Patients with stages I–III mycosis fungoides respond to psoralen and ultraviolet A irradiation (PUVA), or to combinations of PUVA with retinoids or interferon. In contrast, the clinical course of Sézary syndrome is usually aggressive, with an estimated 5-year survival of 11%. A promising new treatment option in this disease is extracorporeal photopheresis [17]. For patients with unspecified primary cutaneous lymphomas presenting as solitary lesions, and ALCL, Sander proposed local radiotherapy and, in cases with multiple lesions, multiagent chemotherapy. Owing to the poor prognosis in blastic NK-cell lymphoma, extranodal NK/T-cell lymphoma, nasal type lymphoma and T-lymphoblastic (LB) lymphoma with skin involvement, multiagent chemotherapy is generally required.

J. Schetelig (Berlin) focused on the development of therapy for AILD, and current high-dose therapy options in this disease. He pointed out that the most difficult objective in AILD is the induction of lasting remissions. W. Siegert and co-workers [18] have demonstrated, in an initial clinical trial, that combination chemotherapy should be the treatment of choice. The complete response (CR) rates in this study, which compared a combination of cyclophosphamide, vincristine, prednisone, bleomycin, adriamycin, procarbacin, ifosfamide, methotrexate and VP-16 (COPBLAM/IMVP-16) versus prednisone, were 59% versus 28%. However, relapses within the first year were frequent. Similar results after chemotherapy were achieved in other studies. Retrospective data from the European Group for Blood and Marrow Transplantation (EBMT), from 29 patients receiving high-dose therapy followed by autologous stem-cell support, demonstrated an improved response rate of 20/29 CRs, compared with 13/29 CRs after conventional chemotherapy before high-dose therapy. Fourteen of the patients received transplants after first-line therapy, and 15 patients after second- or third-line therapy. The 5-year overall survival in this population, estimated from a Kaplan–Meier analysis, was >50%, and in patients who received primary high-dose therapy it was >70%. Schetelig concluded that high-dose therapy is feasible in AILD and should be the treatment standard in relapse, and that further studies are needed to confirm the beneficial outcome in the primarily high-dose-treated population.

M. Reiser (Cologne) reported the retrospective results of a single-center study in 66 patients with T-cell lymphomas, accrued between 1992 and 1997 in Cologne, 28 of whom were diagnosed with PTCL-NOS, 19 with ALCL, 12 with LB T-cell lymphoma and seven with AILD. The overall response rate, following mainly anthracycin-based regimens, was 76%, and the mean overall survival was 8.2 years. The mean survival differed significantly (log rank P = 0.0288) between the T-cell lymphoma subgroups: ALCL 11.1 years; LB 7.1 years; PTCL-NOS 6.6 years; and AILD 1.5 years. Differences in overall survival according to the International Prognostic Index (IPI) were also significant. Additional prognostically unfavorable factors were elevated LDH, B-symptoms and extranodal involvement, all of which showed significant between-subgroup differences in univariate analyses. In their evaluation, advanced stage and bone marrow involvement did not influence the prognosis [19]. Reiser emphasized that in T-cell lymphomas, the histological subtype and risk factors may be more relevant for the estimation of prognosis than the T-cell phenotype alone.

C. Gisselbrecht (Paris) described the development of treatment protocols for PTCL by the Groupe d’Etude des Lymphomes de l’Adulte (GELA). Early studies did not stratify treatment for T- and B-cell lymphomas. In both the LNH84 and the LNH87 trials, the T-cell phenotype was associated with a worse outcome compared with the B-cell phenotype [20, 21], with the exception of ALCL, which was found to have an even better prognosis than high-grade B-cell lymphomas. In the LNH87 study, the outcome of non-ALCL T-cell lymphomas was comparable to that of B-cell lymphomas in patients with an IPI of 0 and 1. Thus, worse results were due to an unfavorable IPI [21]. From their experience, the French group concluded that the induction of CR should be the primary aim in the treatment of T-cell lymphomas. A subgroup of the T-cell lymphoma patients achieving CR within the LNH87 trial was randomized to receive autologous stem cell transplantation versus conventional chemotherapy. In an intention-to-treat analysis, this study did not show differences in survival. Two ongoing trials of the LNH98 study generation are currently in progress: one in patients up to 60 years of age receiving sequential vincristine, prednisone, bleomycin, adriamycin, procarbacin, ifosfamide, methotrexate and VP-16 (COPADM) with dexamethasone (Dexa), or cytarabine and etoposide (CYVE) with Dexa followed by maintenance therapy; and the second in patients >60 years of age receiving etoposide/methylprednisolone/high-dose cytarabine/cisplatin (ESHAP) plus retinoic acid. Preliminary analyses suggest that neither of these regimens improves the outcome of patients with PTCL. Gisselbrecht concluded that the current achievements in PTCL are unsatisfactory. In his opinion, phase II studies with well-defined evaluation criteria represent an adequate approach to the problem. Consequently, intensified standard regimens or high-dose therapy strategies should be further evaluated. Other treatment options to be explored are regimens that encompass standard and experimental procedures, including monoclonal antibodies or other experimental drugs.
The Italian experience of therapy and prognosis of PTCL was presented by P. L. Zinzani (Bologna). First, he described several studies, advancing from single- to multicenter trials, establishing the role of gemcitabine in CTCL. After promising results in a small pilot study [22], a phase II study with gemcitabine at a dose of 1200 mg/m², administered on days 1, 8 and 15 of a 28-day schedule, was conducted. In 44 pretreated patients, an overall response rate of 71% (12% CR) was achieved [23]. Recently, a multicenter study using gemcitabine in primary CTCL has been initiated by the Italian Cutaneous Lymphoma Study Group. Another focus of research, by the Intergruppo Italiano Linfomi (IIL), described by Zinzani, was the retrospective analysis of outcome and prognostic factors in 383 PTCL-NOS patients, most of whom were treated with anthracyclin-based regimens. The 5-year overall survival in this patient population was 44%. In a multivariate analysis, only age, performance status, LDH level and bone marrow infiltration were identified as prognostic indicators. The IIL is now initiating two studies in pretreated patients: one investigating temozolamide in cutaneous T-cell lymphomas and another examining a combination of cyclophosphamide/doxorubicin/vincristine/prednisolone (CHOP) and alemtuzumab (MabCamPath®) in PTCL-NOS.

**Antibody treatment of T-cell malignancies**

M. Gramatzi (Erlangen) discussed the basic requirements for successful antibody therapy in PTCL. Some antibodies have failed to achieve therapeutic responses as a consequence of the remarkable variety of T-cell differentiation stages and antigen expression. For example, the IL-2 receptor CD25 or CD30 are expressed only on a limited number of T-cell tumors. Even the CD3 antibodies are not reactive in all PTCL, and are reactive in only some T-cell acute lymphoblastic leukemia (ALL) cases. In addition, their use in transplant medicine has suggested that even low doses are likely to be associated with severe side effects, although this may not be true for all T-cell lymphomas [24]. Most PTCL and T-cell ALL express the CD7 antigen, with the notable exception of CTCL. The Erlangen group presented results from animal experiments and pilot clinical studies as well as data on a CD7-Pseudomonas exotoxin, suggesting that the CD7 antigen might be an interesting target [25, 26]. The future of new antibody therapies for PTCL is dependent on further multicenter studies using these and other antigens, and the exploration of the mechanism of antibody-mediated cell killing. This should not only allow the optimal target antigen to be established, but also define the appropriate antibody isotype or immune construct.

M. Dyer (Leicester) presented encouraging data from studies with alemtuzumab directed against the pan-lymphocyte antigen CD52 in the management of T-PLL. In this rare disease, the response to conventional chemotherapy is generally poor, with a median survival of only 6–8 months. Before alemtuzumab, the only drug demonstrated to achieve an improved survival was pentostatin [27]. After encouraging results obtained in a pilot study in T-PLL [28], Dyer and co-workers initiated an international study [29] using alemtuzumab 30 mg, administered three times weekly, for up to 12 weeks. Mostly pretreated patients (n = 39), with a median age of 57 years, were enrolled, 24 of whom were chemoresistant. CR was achieved in 23 patients (59%) and partial response (PR) in six patients (15%). The best responses were observed in blood and bone marrow, followed by spleen, skin and lymph nodes. The median overall survival from the start of alemtuzumab treatment was 10 months, and 18 months in patients who had achieved a CR. The toxicity in this trial was acceptable and the response was better than with pentostatin; however, alemtuzumab was not found to be curative [29]. Consequently, Dyer suggested that in T-PLL, alemtuzumab may allow patients to progress to autologous or allogeneic stem cell transplantation, and that transplantation should be considered early in first remission, in order to consolidate responses.

Experiences with alemtuzumab in other T-cell malignancies were presented by R. Repp (Erlangen), who had previously participated in two Swedish trials, one in mycosis fungoides/Sézary syndrome (MF/SS) and one in advanced other PTCL. In the MF/SS trial, patients who required treatment, with documented failure to PUVA and a history of up to five previous systemic therapy regimens, were eligible. Twenty-two patients with stage II (three), stage III (10) and stage IV disease (nine) with MF/SS were included. Alemtuzumab 30 mg was administered three times weekly, for up to 12 weeks. An overall response of 55%, with 32% CR, was achieved. The median time to treatment failure was 12 months. Hematological toxicity was moderate. Non-hematological adverse events (mostly grade I and II) included fever, rigors, nausea, hypotension, rash, fatigue and bronchospasm. Four patients with reactivated cytomegalovirus had fever but no signs of pneumonitis, and responded to gancyclovir. A phase II study in relapsed or refractory patients with PTCL was stopped after the accrual of 14 patients because of treatment-associated toxicity, especially severe infections. However, three CRs and two PRs were documented, resulting in a response rate of 36%. The regimen established as safe and effective in chronic lymphocytic leukemia (alemtuzumab 30 mg, three times weekly) is effective but has higher toxicity in patients with heavily pretreated PTCL; therefore, Repp suggested that a dose and/or schedule optimization seems to be necessary. Conversely, the standard three-times-weekly alemtuzumab schedule is a feasible and highly effective treatment option in patients with primary CTCL.

**Introduction of current treatment studies in peripheral T-cell lymphomas**

C. Kahl (Rostock) outlined the design of a study by the East German Study Group Hematology and Oncology, using high-dose therapy with autologous or allogeneic stem-cell transplantation for patients with a primary diagnosis of PTCL, as follows: high-risk patients (IPI 2–3, bulky disease or bone marrow infiltration) will be treated with four cycles of CHOP. Allogeneic stem-cell transplantation will be performed in patients <50 years of age, with an identical sibling or an unrelated donor, if they have achieved CR or PR. Patients without a donor and those between 50 and 60 years of age will receive autologous stem-cell support after myeloablative therapy. Almost all patients with PTCL, including MF/SS (stage III and IV), are eligible for inclusion.
Only patients with ALK+ ALCL will be excluded, as they have an excellent prognosis with CHOP-like therapy. Other exclusion criteria are pretreatment and Eastern Cooperative Oncology Group (ECOG) performance status >2. A scientific program, consisting of histopathological, cyogenetic and molecular genetics analyses, will supplement the study.

Preliminary results of a similar, already active study were reported by M. Wilhelm (Würzburg). After four to six cycles of CHOP followed by dexamethasone, carmustine, etoposide, ara-C, melphalan (Dexa-BEAM) and stem-cell apheresis, patients (≥65 years of age) undergo myeloablative therapy with high-dose cyclophosphamide and autologous stem-cell transplantation. Patients >65 years of age receive eight cycles of CHOP. The study is open to patients with all types of T-cell lymphoma except ALK+ ALCL, primary CTCL and precursor T-cell lymphomas.

The aims of the study are the evaluation of efficacy and risk parameters, and lymphoma cell characterization by immunohistochemistry, fluorescence-activated cell sorting analysis and molecular biology. At the time of writing, 37 patients had been included, 20 of whom were evaluable for response and toxicity. Of these, 14 patients (70%) had achieved CR (seven PTCL-NOS, six AILD, one ALCL), stable disease was noted in one patient and progressive disease in five patients: PTCL-NOS (one); AILD (one); ALCL (two); and enteropathy-type PTCL (one). Five patients died during therapy and one patient relapsed after achieving CR. Two deaths were related to treatment-associated toxicity. Otherwise, toxicity was noted as within the expected range.

As a consequence of the promising results of sequential high-dose therapy in patients with high-grade lymphomas and unfavorable prognosis (IPI 2–3) in the mega-cyclophosphamide, doxorubicin, vincristine, etoposide, prednisolone (CHOEP) trial (German Study Group High Grade Lymphomas), L. Trümper (Göttingen) suggested including intermediate-high and high-risk patients with PTCL in this trial. For PTCL patients with low and low-intermediate risk according to IPI, he proposed a more conservative approach. Patients receiving treatment according to the proposed protocol would receive 6–8 cycles of CHOP-14 (14-day regimen), as CHOP-14 was demonstrated to be superior to CHOP-21, especially in high-grade lymphomas with a high proliferation rate. Those patients achieving CR or PR would undergo consolidation therapy with alemtuzumab 30 mg, once weekly. Inclusion criteria would be patients with histologically confirmed PTCL-NOS and AILD, 18–70 years of age, with a low or low to intermediate prognosis according to the IPI in patients under the age of 60 years. A scientific program including cyogenetics and molecular genetics, and gene expression microarrays would be integrated into the protocol.

A recently activated study was introduced by E. Weidmann (Frankfurt/Main) for the Study Group Peripheral T- and NK-Cell Neoplasias. According to this protocol, patients are treated with chemoimmunotherapy consisting of alemtuzumab, fludarabine phosphate (Flu; Fludara®), cyclophosphamide (CP) and doxorubicin (Dox) (Campath-FCP® regimen) as follows. First cycle: alemtuzumab 3, 10, 30, 30 mg (escalating doses), days 1–4; Flu 25 mg/m², days 2–4; CP 600 mg/m², day 3; and Dox 50 mg/m², day 4. Cycles two to six (repeated every 3 weeks) are the same as cycle 1 but without the 3-mg dose of alemtuzumab on day 1 of the first cycle. The rationale for this study design was the proven efficacy of CP and Dox, the excellent results with the combination of Flu and CP (FC) in other lymphomas, and the possible synergy in combinations of antibodies with cytotoxic drugs. Furthermore, in contrast to continuous alemtuzumab therapy, the regimen may allow the partial reconstitution of the immune system between the cycles. Inclusion criteria are histologically confirmed PTCL (except primary cutaneous and ALK+ ALCL) at initial diagnosis and in first relapse. The study group includes a scientific program analyzing histopathology and molecular pathology, cyogenetics and molecular cytogenetics, immunology, TCR signaling and apoptosis pathways. At the time of writing, five patients had been included, but it is too early for an evaluation of the treatment outcome.

The four studies were extensively discussed among all participants of the workshop. Agreement was reached that, at present, there is no standard in PTCL which could serve as a good basis for therapy optimization. Several participants proposed intensive cooperation between the two high-dose therapy studies. Moreover, there was general agreement to regularly exchange experiences between the four studies, with the objective of establishing a common strategy for the treatment of PTCL in Germany. A final discussion of such a strategy is planned after finalization of the current phase II studies. Since a long-term aim must be the initiation of international trials in these rare diseases, study groups from other countries will be explicitly invited to participate in this discussion.

Conclusions

The best approach for treating patients with PTCL is still unknown, as a consequence of the minimal research effort, until recently, in these diseases. Results from studies in which both T- and B-cell lymphomas were included have generally demonstrated a worse outcome for patients with PTCL, compared with B-cell lymphomas [21, 22]. The even poorer survival data derived from consecutively analyzed patient populations is indicative of a high frequency of positively selected patients in clinical studies. The latter may be the result partly of diagnostic difficulties and partly of the uncertainty in how to manage the individual patient [2].

Despite the unfavorable prognosis in the majority of patients with PTCL, little has been done to establish treatment standards to improve patient outcome. Treatment approaches range from ‘watch-and-wait’ to many different therapeutic options, including steroids, alkylating agents, other monotherapies, combination chemotherapy and high-dose therapy, which are often used irrespective of prognostic factors. A resolution of this issue will only be possible by clinical and experimental research involving many different disciplines. From a clinical point of view, it is vital to evaluate current trials, and to initiate new phase II studies for the collection of data on the efficacy of different drugs or regimens. It is also essential to increase the knowledge base on epidemiology, clinical presentation, prognostic factors and patient outcome. Improvement of the techniques for disease characterization by

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histopathology, molecular pathology, cytogenetics and molecular genetics, which were the subject of intense discussion at this workshop, is also a vital requirement. Finally, experimental research with the aim of understanding the development and pathophysiology of PTCL is necessary to support the development and establishment of new treatment strategies. All these aims can only be achieved by the rational, controlled inclusion of patient groups in clinical and scientific programs, and by the interaction of researchers from many different disciplines.

The authors hope that the workshop ‘Diagnosis and Actual Therapy Strategies in Peripheral T-Cell Lymphomas’ may have laid the foundation for achieving these challenging aims, and invite interested colleagues from all geographical and scientific areas to participate.

Acknowledgements

The authors thank the participants of the workshop for their contributions, namely: M. Bentz, Ulm; B. Dörken, Berlin; M. Dreyling, Munich; M. Dyer, Leicester, UK; A. Engert, Cologne; C. Gisselbrecht, Paris, France; M. Gramatzki, Erlangen; M. Hallek, Munich; M.-L. Hansmann, Frankfurt; C. Kahl, Rostock; W.-D. Ludwig, Berlin; P. S. Mitrou, Frankfurt; H. K. Müller-Hermelink, Würzburg; C. Peschel, Munich; M. Reiser, Cologne; R. Repp, Erlangen; T. Rüdiger, Würzburg; A. Sander, Munich; J. Schetelig, Berlin; R. Siebert, Kiel; L. Trümpfer, Göttingen; M. Wilhelm, Würzburg; A. Zettl, Würzburg. The authors thank MedacSchering Onkologie GmbH, Munich, for supporting the workshop.

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