7. Henry Rappaport Memorial Lecture

ANTIGEN RECEPTOR AND BAFF RECEPTOR MEDIATED SURVIVAL OF NORMAL AND MALIGNANT B CELLS
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In this lecture I will summarize work from my own and other groups indicating the central role of signals delivered through the B cell antigen receptor (BCR) and the BAFF receptor (BAFFR) in keeping mature B cells alive in vivo. While the signals through the BCR may either be due to interaction of the BCR with antigen or reflect constitutive BCR signaling, BAFFR signaling is triggered by the survival factor BAFF, produced by cells of the myeloid lineage and member of the tumor necrosis factor family. Both receptors are connected to the NFκB signaling pathway, and NFκB signaling is itself crucial for mature B cell survival. Interestingly, there is substantial evidence that both BCR and NFκB signaling play a fundamental role also in the pathogenesis and maintenance of mature B cell lymphomas in the human. I will describe approaches to model such lymphomas in the mouse by methods of transgenesis and, specifically, conditional gene targeting, opening the way to a detailed analysis of the extent to which their maintenance depends on the same survival signals identified in their non-transformed counterparts.
LATE EFFECTS AFTER HODGKIN'S DISEASE: RECOMMENDATIONS FROM THE ROCKEFELLER FOUNDATION SPONSORED WORKSHOP ON REDUCING MORTALITY AND IMPROVING QUALITY OF LIFE IN LONG-TERM SURVIVORS OF HODGKIN'S DISEASE. BELLAGIO, ITALY, JULY 9-16, 2003

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A Rockefeller Foundation sponsored workshop was held from July 9-16, 2003 in Bellagio, Italy to develop strategies for surveillance and prevention to improve the quality of life and survival in patients cured of Hodgkin's disease. Findings from the workshop as well as more recent advances will be highlighted in this presentation. The workshop was attended by 18 epidemiologists, medical oncologists and radiation oncologists from North America, Europe and Asia. A detailed program with preliminary information was provided to the participants prior to the meeting. The first 3 days of the workshop focused on recently published and unpublished data. This information was then utilized in the working groups held during the last 3 days. A summary of the workshop will be published in the European Journal of Cancer in 2005. Current institutional and cooperative group data was presented on excess mortality, on the excess incidence of cardiac disease and second malignancy, and on decreased health-related quality of life in survivors of Hodgkin's disease. Data was available for patients followed out to 30 years after Hodgkin's disease. We identified prognostic factors for the development of late mortality; these included both treatment-related risk factors (i.e., type and extent of chemotherapy and radiation therapy) and patient-related factors (i.e., age at treatment, genetic history, smoking history). Enumeration of treatment-related and patient-related factors will provide the basis for developing research proposals and clinical guidelines for the long-term follow-up of patients. Specific prevention and early detection strategies based on risk were outlined at the workshop. For example, tamoxifen, a drug known to be effective in the treatment of breast cancer, was proposed as a strategy for the reduction of excess breast cancer risk using retrospective and prospective data and modeling by decision analysis. Data was also presented evaluating the use of computed tomographic screening for the detection of lung cancer in patients having both the risk factors of smoking and medical irradiation. Recently, an international trial has been proposed to prospectively study this question. Data also was presented on the challenges to the delivery of health-care in developing countries were discussed with specific data presented from India, China and Central America.

Four working groups (second malignancy, cardiac dysfunction, other effects, and treatment reduction) were held the last three days of the workshop. The working groups identified the following areas where additional work is needed:

1. Continued ongoing research (risk prediction, risk reduction, managing survivors through screening, prevention and treatment, research priorities, research methods, research partnerships, and research in developing countries).
2. Recommendations for current clinical practice (follow-up studies, screening, and prevention).
3. Recommendations to improve the education of physicians and patients.

A two-hour follow-up workshop was held at the Hodgkin's Disease meeting in Cologne Germany in September 2004 where investigators provided updates on new and ongoing protocols on late effects in Hodgkin's disease survivors. These presentations included proposals for developing biological markers for second malignancies and presentation of recent prospective cardiac projects. Data now suggests that the risk of cardiac disease can be reduced by aggressively managing other cardiac risk factors in long-term survivors. A summary or recent data and trials will also be presented.

Elderly patients with Hodgkin's lymphoma (HL) have a poorer outcome due to treatment-related mortality when treated with more aggressive approaches: Results of the studies HD5-HD9 performed by the German Hodgkin Study Group (GHSG)

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Introduction: With improved prognosis of patients with Hodgkin's lymphoma (HL), interest increasingly focuses on high-risk groups such as elderly patients. However, little information is available from randomized studies. We thus performed a retrospective analysis of the German Hodgkin Lymphoma Study Group (GHSG) database to determine clinical presentation, toxicity of treatment and outcome of elderly HL patients.

Methods: A total of 4251 patients included in the GHSG studies HD5-9 were analysed of whom 372 (8.8%) were 60 years or older and 3879 (91.2%) were younger than 60 years.

Results: Statistically significant differences were seen in patient characteristics including histology, B-symptoms, ESR, large mediastinal mass, bulky disease and Karnofsky index. Acute toxicity during chemotherapy was higher in elderly patients (87% vs 79%). The most obvious difference was observed for severe infections (17% vs 6%). The significantly higher rate of infections was due to more severe leukopenia in elderly patients (grade IV: 41% vs 25%). As a result, significantly fewer elderly patients received at least 85% of intended chemotherapy dose (74% vs 90%). At a median follow-up of 65 months, 38% and 11% of patients respectively died. The survival analysis showed a statistically significant poorer prognosis for elderly patients in terms of 5-year OS (65% vs 90%), FFTT (66% vs 79%) and Hodgkin specific FFTT (74% vs 82%).

Conclusion: Elderly patients have a poorer risk profile compared to younger HL patients and experience more severe treatment-associated toxicity. Higher mortality during treatment as well as lower dose-intensity are the major factors explaining the poorer overall outcome of elderly Hodgkin lymphoma patients.
TREATMENT AND OUTCOME IN ADOLESCENTS AND YOUNG ADULTS (AYA) WITH INTERMEDIATE AND AGGRESSIVE NON-HODGKIN'S LYMPHOMA (NHL)

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The incidence of NHL in adolescents (15–19 yrs) and young adults (20–30 yrs) (AYA) is 7–8% per year of malignant tumors, ranking fourth behind HD, GCT and CNS malignancies. NCIC SEER and UK cancer registries data suggest that approximately 10 cases/10^5 AYA occur each year. While the incidence of cancer has been rising by about 0.9% per year in adolescents, the incidence of NHL has had even a greater increase (2.0%). The majority of NHL in AYA patients have an intermediate (DLBCL, ALC) or aggressive histology (BL, LL). Unfortunately, only 5–20% of AYA patients with malignant disease are treated on institutional or cooperative group clinical trials compared to children <14 yrs (80–100%). Recent results from PAB and BFM cooperative group studies in adolescents with localized and advanced DLBCL and BL have a 95% and 80–90% OS, respectively. However, cooperative group clinical trials in young adults with DLBCL and BL are still lacking. AYA pts with PMBL/BLCL have a poorer outcome with only 60–70% OS. Pediatric and adult clinical trials in advanced ALCL in AYA suggest a 60–70% OS (ALK-≥ALK+). The results in adolescents with limited stage LL is about 85–90% OS but in young adults, only 45–60% OS. Furthermore, in adolescents with advanced stage LL, the prognosis is 80–90% OS compared to young adults of 50–60% OS. Few comparative studies have been performed to compare the genetics and biology of AYA NHL with childhood or adult NHL with similar morphologic histologies. Furthermore, it is unknown whether pediatric vs. adult clinical strategies are best in AYA NHL. Future research and collaborations with pediatric and adult cooperative groups is required to improve our understanding of the biology and best treatment strategy for AYA with NHL.
9. Chronic Lymphocytic Leukaemia

036

CLL SUBGROUPS CARRYING GENETIC HIGH-RISK FEATURES SUCH AS 11q-, 17p-, OR V-21 USAGE SHOW A HIGH RATE OF DISCORDANT VH AND ZAP-70 STATUS


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The VH status is a strong prognostic marker in CLL. ZAP-70, a zeta associated tyrosine kinase physiologically expressed by T-cells, is overexpressed in VH unmutated CLL and could therefore serve as a surrogate marker for the VH status. We analyzed ZAP-70 expression (n = 146). The VH status (n = 118) and genomic aberrations (n = 139) in a single center CLL cohort to study associations among these parameters and to assess their relative prognostic value. ZAP-70 expression was measured by 4-color flow cytometry (CD5, CD19, CD3/56, ZAP-70) applying an unconjugated anti-ZAP-70-antibody (Upstate, clone ZF.3.2) according to Crespo et al., NEJM 2003. ZAP-70 expression was positive (cut-off 20%) in 55% and negative in 45% of cases. VH was mutated in 36% and unmutated in 64% of cases. Overall, ZAP-70 expression predicted the VH status in 75% of cases. When analyzing the association of the VH status and ZAP-70 expression in distinct genetic subgroups the proportions with a concordant VH and ZAP-70 status were strikingly different: V-21 6/13 (46%), 17p- 11/16 (69%), 11q- 15/26 (58%), 13q- as a single aberration in 11/23 (48%), excluding V-21 3/27 (84%) and normal karyotype 28/31 (90%). The majority of cases carrying a mutated V-23 gene showed high ZAP-70 expression (69%, 67%). In the subgroups defined by high risk genomic aberrations (including V-23 and excluding 17p-, 13q-, 11q-) the majority were VH unmutated (35/42, 83%) and 13q- as a substantial proportion of cases exhibited low ZAP-70 expression (17p- 6/61, 38%, 11q- 9/26, 35%). Within a median follow up time of 48 months (in) the treatment free survival (TFS) and overall survival (OS) of the ZAP-70 pos. neg. cases were 26 vs. 58 months (P = 0.007) and 100 vs. not reached (P = 0.006). In the subgroups V-23, VH unmutated and VH mutated the TFS and OS were 17 vs. 26 months. Within a median follow up time of 48 months (in) the treatment free survival (TFS) and overall survival (OS) of the ZAP-70 pos. neg. cases were 26 vs. 58 months (P = 0.007) and 100 vs. not reached (P = 0.006). In the subgroups V-23, VH unmutated and VH mutated the TFS and OS were 17 vs. 26 months. For the V-21 group all 4/10 cases who received therapy within follow up exhibited a V-21 gene (3/4) or a 17p deletion (1/4). In summary, ZAP-70 expression correlated with an unmutated VH in our series. The proportion of discordant cases was particularly high when V-23 usage (ZAP-70 pos./VH mutated) or high risk genomic aberrations were present (ZAP-70 neg./VH unmutated). These findings implicate a complementary prognostic impact of ZAP-70 expression, VH status and genomic aberrations. Furthermore these data point to genetic high risk features such as 11q-, 17p- and V-21 usage as sources of discordances between VH status and ZAP-70 expression.

037

NEW PERSPECTIVES FROM THE NEW BIOLOGY OF CLL

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All crucial events in the natural history of CLL occur in tissues. CLL cells are highly dependent on the external stimuli provided by the microenvironment (e.g. antigen stimulation, stromal support, T cell help). The CLL proliferating reservoir that replenishes the accumulation compartment is represented by focal aggregates (pseudofollicles -PF-). of prolymphocytes and paramonoblasts in lymphnodes and bone marrow. Proliferating cells differ from circulating resting leukaemic cells by the expression of apoptosis-regulator molecules like Survivin, chemokinies like CCL-17 and CCL-22, proliferation-related genes like Kif7. CLL PF are however less likely to be abnormally connected to many express CD40Ligand. The different accessory cells present within the infiltrated tissues provide the malignant clone with a different support in terms of onset and duration. T cells provide a short term support and stromal cells a long term survival effect.

Despite a distinctively unique phenotype (CD5-, CD23+, slp+), CLL is heterogeneous as for molecular features such as somatic mutations in the immunoglobulin variable region (IgVH) genes, expression of CD38 and of the tyrosine kinase ZAP-70. At functional level the heterogeneity of CLL is highlighted by the presence or absence of response to stimulation via cell surface receptors such as the B-cell receptor (BCR), CD5 and CD40. The emerging concept, supported by a proteomic approach with mass spectrometry, protein sequence and western blot analysis, is that the malignant cell capacity to effectively respond to the stimulation of BCR may favour a more aggressive and unfavourable course. These data reinforce the concept that the molecular definition of patients is crucial to assess their prognosis and clinical evolution.

038

FIRST LINE THERAPY OF CLL, UPDATE 2005

Michael Hallé, on behalf of the German CLL Study Group

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The last 15 years have seen a dynamic development of new compounds for the treatment of CLL. Two monoclonal antibodies (rituximab and alemtuzumab) have become available for the treatment of CLL, and additional antibodies (anti-CD23, anti-MHC II) as well as other new drugs are currently tested in phase I or II trials. The increased experience with autologous and allogeneic progenitor cell transplantation allows to offer these treatment modalities to physically fit patients at very high risk or at relapse. However, the optimal timing of these more intensive treatment modalities remains unclear.

New prognostic parameters like molecular genetics (fluorescent in situ hybridization, immunoglobulin mutation status), serum parameters (β2-microglobulin, thymidine kinase, CD23), immunophenotyping (ZAP70, CD38), and the careful assessment of disease activity allow a more precise prediction of an individual patients' prognosis, independent of the Binet or Rai staging.

It is our challenge to use these different tools for a new, optimized, risk adapted strategy of CLL management during the next decades, with the aim to achieve long-term remissions or even cure of this disease. At the same time, the treatment should preserve a good quality of life. The presentation will summarize the current status of the various treatment options for CLL. Moreover, the actual treatment algorithm of the German CLL study group, which is adapted to both prognostic factors and the physical fitness of the patients, will be presented.

039

CHEMOIMMUNOTHERAPY OF CLL - A NEW GOLD STANDARD

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In vitro data suggest that rituximab (R) makes lymphoid neoplastic cells more sensitive to the cytotoxic effects of chemotherapy. In addition the purine analogues fludarabine complement defense proteins CD46, CD55 and CD59 presumably enhancing the complement-mediated cytotoxicity of Rituximab. Randomized studies have demonstrated that fludarabine and cyclophosphamide (FC) are more effective than fludarabine (F) as a single agent in achieving complete remissions (CR) and prolonging progression-free survival (PFS). Major chemoimmunotherapy regimens have been developed combining R with fludarabine (FR) and the two drugs combined with cyclophosphamide (PCR). CALGB was the first to demonstrate an increase in CR rate and in sequential study analysis an improvement in disease free survival and overall survival when R was added to F. The CR rate at the end of FR followed by R consolidation was 47% vs. 28% for F followed by R consolidation. The combination of FCR has been used extensively at MDACC as induction and salvage therapy for CLL. Three hundred patients have received FCR as initial induction therapy for patients requiring therapy using NCICWG criteria. CR was obtained in 73% nodular PR (NPR) 10% and NR in 12%. Pretreatment characteristics associated with CR in a multivariate analysis include age < 70 years, white blood cell

Comparison of FCR with FCR in MDACC Studies

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Years</th>
<th>Pts.</th>
<th>CR%</th>
<th>TTP (Med)</th>
<th>Surv (Med)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC</td>
<td>1993-1999.5</td>
<td>52</td>
<td>46</td>
<td>48 mths</td>
<td>100 mths</td>
</tr>
<tr>
<td>FCR</td>
<td>1993.5-2003</td>
<td>300</td>
<td>73*</td>
<td>54+ mths*</td>
<td>58+ mths*</td>
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* P < 0.001; * P = 0.06
count < 200,000/μl, hemoglobin >13 G%, and beta-2-microglobulin < 4 mg/l. Comparison of FCR vs. PC in several MDACC studies showed a significantly higher CR rate in proportionate patients developing flow cytometry in remissions and longer time-to-progression in the FCR group (P < 0.001).

With a minimum of 1.5 years follow-up, the five year survival and is projected to be 77% and 3 years time-to-treatment failure 61%. FCR negativity for IgVλ was obtained in 9/160 (43%) and CD5+ CD19 coexpressions of <1% in marrow in 165/209 (79%) of CR patients. Both FCR negativity and marrow CD5+ CD19 coexpression < 1% correlated strongly with remission duration (P < 0.001).

The high CR rate and long time-to-progression and survival of the FCR regimen led to a comparison of historical preceding studies of FC and F. Multivariate analysis showed that FCR was the dominant characteristic associated with improved survival in frontline studies. Similar results are obtained when FCR is compared with F or PC in salvage studies. Together with the development of consolidation therapy with alemtuzumab and allogeneic bone marrow transplantation suggests that curative strategies can be developed for patients with progressive CLL.

**COMBINATION CHEMOTHERAPY WITH FLUDARABINE, CYCLOPHOSPHAMIDE AND MITOXANTRONE (FCM) INDUCES A HIGH RESPONSE RATE IN PREVIOUSLY UNTREATED CLL**


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Treatment with FCM results in response rates of 60% in relapsed or refractory CLL. Against this background, we started a trial of FCM in patients with CLL younger than 65 yrs. FCM consisted on fludarabine 25 mg/m² i.v. on days 1 to 3, cyclophosphamide 200 mg/m² i.v. on days 1 to 3, and mitoxantrone 60 mg/m² i.v. on day 1 given at 4-week intervals up to six courses. Response was assessed two months after treatment and included bone marrow and minimal residual disease (MRD) analysis by four-color flow cytometry and FCR. Of the fifty-seven patients (74% male, median age 57 years) evaluable for response, 85% were in advanced (B and C) Binet's clinical stage and 62% had increased (>20%) ZAP-70 expression. Cytogenetic and FISH analysis disclosed normal karyotype in 32%, isolated 13q (18%), +12 (20%), -11q (16%), -17p (6%), and others (8%). 91% of the patients could receive the entire planned treatment. The overall response rate was 91%; CR with negative MRD was obtained in 27%, CR in 23%, PR in 18%, and PR in 20%. Duration of response was 55% at 36 months. Hematological toxicity was mild, with 16% grade II neutropenia. Fever was observed in 3% of the courses. Two patients developed a fulminant hepatitis of viral origin, one of them dying as a direct consequence. In conclusion, in patients with CLL previously untreated, FCM induces a high CR rate, including an important number of MRD negative CR. This places FCM among the most effective regimens for CLL.

**EFFECTIVENESS OF SUBCUTANEOUS ALEMUTUMAB (CAMPATH-1H) IN GENETIC HIGH-RISK, FLUDARABINE-REFRACTORY CLL: CL2H STUDY OF THE GERMAN CLL STUDY GROUP (GCLLSG)**


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Fludarabine-refractory CLL has a poor prognosis after chemotherapy with a median survival time of less than 12 months. Intravenous Campath-1H (Alemutumab) was approved for fludarabine refractory CLL based on a remission rate of 33% and a median survival time of 16 months (Keating et al., Blood 2002). The CL2H trial of the GCLLSG was initiated to evaluate the subcutaneous application of 3 x 30 mg Campath-1H weekly in fludarabine refractory CLL after intravenous dose escalation. The current interim analysis is based on the first 50 consecutive patients enrolled until April 2004. Median age was 62 (35–79) years, 74% were male, and a median number of 4 (1–9) prior lines of therapy had been given. Intravenous dose escalation was accompanied grade 1–II rigors and fever after premedication with paracetamol and antihistamines in the majority of patients, while grade III/IV infusion reactions were rare (n = 3). Subcutaneous treatment was continued on an outpatient basis in all cases except for 29 patients due to neutropenia/neutropenia (n = 15), anemia (n = 3), infections (n = 3, CMV reactivations n = 2), and was stopped early in 26 cases due to no response (n = 12), CMV reactivation (n = 3), hematotoxicity (n = 7), and infection (n = 4). The median Campath-1H administration was 839 (6–1981) mg. During subcutaneous treatment toxicity was mostly grade III apart from hematotoxicity (grade III/IV anemia: 24%, thrombocytopenia: 50%, neutropenia: 67%) and grade III/IV infections (35%). After a median follow up time of 12.2 months 18 deaths have occurred (progression n = 11, sepsis n = 4, not CLL related n = 2, before treatment start n = 1). The overall response rate was 37% (CR 4%, PR 33%). The median progression free survival time was 10.8 months, and median overall survival time was 17.4 months. Genetic high-risk factors were present in the vast majority of cases (73% unmutated VH, 30% (7p- 21q- 11q- 18q- 12q). Responses (CR or PR) were observed in 38% of VH unmutated, 33% of 11q-, 38% of +12, and 46% of 1p+ cases. In conclusion, subcutaneous Campath-1H is feasible in an outpatient setting in a high-risk population of fludarabine-refractory CLL and appears to be of similar efficacy as by intravenous administration. Most importantly, genetic high risk subgroups with unmutated VH, 11q- or 1p+ appear to respond to Campath-1H. An amendment has been activated including prophylactic pneumonia treatment and allowing subcutaneous dose escalation in patients of this trial with ongoing recruitment and extended follow-up will be presented.

**LONG-TERM DISEASE CONTROL OF POOR PROGNOSIS CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) BY ALLOGENEIC STEM CELL TRANSPLANTATION (SCT) WITH NONMYEOABLATIVE CONDITIONING (NST): INTERIM RESULTS OF A PROSPECTIVE STUDY**

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The purpose of this study was to investigate prospectively feasibility, toxicity and efficacy of NST in patients with poor-risk CLL.

Methods: Patients younger than 65 years were eligible if they had stage C disease in the presence of an unfavourable VH status, were fludarabine refractory, or had relapse after auto-SCT. Conditioning consisted of daily fludarabine 30 mg/m² and cyclophosphamide 500 mg/m² over 5 days. GVHD prophylaxis was performed with CSA/MTX/ATG. Donor lymphocyte infusions (DLI) were administered from day +100 onwards in case of incomplete chimerism or residual disease. Besides clinical endpoints, minimal residual disease (MRD) was assessed by sensitive (1 tumor cell in 10⁶) 4-colour flow cytometry or clone-specific RQ-PCR.

Results: As of December 2004, 42 patients were accrued including 8 patients from a pilot phase with follow-up information available for 37. Patients had received 4 (1–11) regimens within 53 (6–163) months from diagnosis to transplant. An unfavourable VH status was present in 94% of the patients, and 42% had an unfavourable FISH karyotype (del 11q22 or del 17p13). 42% were refractory to fludarabine, due to response to monoclonal antibodies, however, 83% were in partial or complete remission at NST. Allografts were obtained from HLA-identical related (n = 21) or unrelated donors (n = 16). Grade II/IV acute GVHD occurred in 43% and chronic GVHD in 63% of patients at risk. With 21 (1–64) months of follow-up, 3-year treatment-related mortality (TRM), relapse incidence and overall survival were 6%, 28% and 84%, respectively. Only 2 relapses were observed later than 2 years after NST. The probability of being alive and MRD-negative 1 year post transplant was 66% with a median time to MRD negativity of 9 months. MRD negativity at 1 year was highly predictive for durable remission with only one relapse occurring in this subset, whereas all patients being MRD-positive relapsed except for 2 individuals who could be converted to MRD negativity by DLI. The only other variable predicting relapse was refractory disease at NST, whilst FISH karyotype, fludarabine resistance, and donor type had no impact.

Conclusions: In poor-risk CLL, NST as used here is not only partly but mostly by a TRM that is comparable and by an efficacy that is clearly superior to any
other salvage regimen. Approximately two thirds of the patients can achieve MRD negativity at one year post transplant, which is a strong predictor of long-term disease control and possibly cure.

OUTCOME IN PATIENTS WITH RICHTER'S SYNDROME TREATED WITH CHEMOTHERAPY AND/OR IMMUNOTHERAPY WITH OR WITHOUT STEM CELL TRANSPLANTATION

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Introduction: The clinical outcome of patients with Richter's syndrome (RS) is poor. The purpose of this study was to assess the incidence, presenting characteristics, and the treatment outcomes in patients with RS.

Methods: We performed an electronic database search of patients with chronic lymphocytic leukemia (CLL) or RS who presented at The University of Texas M. D. Anderson Cancer Center.

Results: Between 1/83 and 12/03, 186 with RS and 3065 patients with CLL were registered. The median age of patients with RS was 60 yrs (range 29–82). There were 129 men. The median time from CLL to RS was 4.2 yrs (range 0–29.4). The median baseline β2-microglobulin (β2-M) level was 3.8 mg/L (range 1.3–25.3), and the median LDH level was 806 IU/L (range 209–33,321). Patients (n = 128) were treated with chemotherapy/immunotherapy (C/I) followed by autologous stem cell transplantation (allo-SCT) (n = 13), chemotherapy (C/T) followed by autologous (auto) or allo-SCT (n = 9), C/T alone (n = 45), C/T alone (n = 73), or other treatments (n = 8). Patients treated with C/T followed by allo-SCT had higher rates of overall response (OR 85%, CR 31%) than patients treated with C/T+auto-SCT or allo-SCT (OR 78%, CR 22%), C/T alone (OR 40%, CR 11%), C/T alone (OR 30%, CR 8%) or other therapies (OR 25%). The median follow-up of surviving patients was 21 months. The 2-year overall survival rate was higher in the C/T + allo-SCT group (52%) than the other four groups (30%, 18%, 14% and 25%, respectively). The 2-year failure-free survival rate was higher in the C/T + allo-SCT group (52%) compared with the other groups (17%, 9%, 12% and 12%, respectively). High LDH levels (≥1.5 × upper limit of normal) and high β2-M levels (≥2.6 mg/L) were associated with shorter survival (P = 0.001 and P = 0.04, respectively).

Conclusions: C/T followed by allo-SCT was associated with higher response, failure-free survival, and overall survival rates than the other therapies (P = 0.04, P = 0.03 and P = 0.02, respectively). High LDH and β2-microglobulin levels at presentation are associated with poor survival in patients with RS. RS patients should be treated with induction C/I, followed by allo-SCT. Post-remission therapy with allo-SCT appears to be critical in maintaining remission and prolonging survival and, therefore, should be offered to patients with available donors.
10. Is R-CHOP the Standard Treatment for DLCL?

CONTROVERSY II: R-CHOP IS NOT THE STANDARD TREATMENT FOR DLCL

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Rituximab has been demonstrated to improve results in young good-prognosis when combined to a CHOP-21-like chemotherapy compared to chemotherapy alone (MInT trial). Rituximab was also shown to improve the results of elderly patients with aggressive lymphomas when combined to CHOP-21 compared to CHOP-21 alone. These results made many people generalize and recommend rituximab in combination with chemotherapy for all patients with aggressive lymphomas. Such a non-critical attitude is gains wide-spread approval in light of the favorable toxicity profile of rituximab. However, several questions remain: While rituximab works well in patients with a good-prognosis profile, this is less the case in patients with a poor-prognosis profile. In particular, it remains to be shown that patients with bcl-2 positive aggressive lymphoma profit at all from the addition. Historical comparisons of two series of chemotherapies that are more intensive than CHOP in young high-risk patients fail to show any advantage from the addition of rituximab to these regimen, indicating that the lack of rituximab effect in this population might be due to the particular biology of these tumors or because any positive effects of rituximab that emerge when combined with less intensive regiments like CHOP-21 can be compensated by increasing the dose-intensity of the respective chemotherapy. In a similar direction point the interim results of the ROCH114 trial that showed that when combined with a dose-dense regimen like CHOP-14 the effects of rituximab are considerably smaller in elderly patients than those observed in the GELA trial when combined with CHOP-21, if they exist at all. While randomized trials to determine the value of rituximab in the discussed subgroups might not be easy to perform, they are necessary in order to avoid unnecessary costs of a drug, the long-term side effects of which are largely unknown.

CONTROVERSY II: R-CHOP IS THE STANDARD TREATMENT FOR ADVANCED STAGE, DLCL

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The recent incorporation of rituximab (R) monoclonal antibody into standard CHOEP chemotherapy represents an improvement in overall survival for patients with DLCL-B. The GELA group randomized previously untreated elderly patients with DLCL-B to receive either 8 cycles of CHOP or R-CHOEP. R-CHOEP led to significant prolongation of EFS and OS with no increased toxicity. A North American study randomized elderly patients to receive initial therapy with either CHOP or R-CHOEP given on a different schedule. Responding patients were then randomized to receive either R maintenance therapy (4 doses q 6 months x 2 years) or no maintenance. Results show a PFS benefit for the group initially randomized to R-CHOEP (p = 0.05) without an OS benefit. While R maintenance therapy benefited all patients, a subset analysis demonstrated no benefit to maintenance R for patients who received initial treatment with R-CHOEP. The trial is difficult to difficult to analyze for OS because of this demonstrable interaction between the induction and maintenance. A weighted analysis was performed to mathematically model two groups being treated only with CHOP or R-CHOEP; an OS benefit was then seen with R-CHOEP. Thus this study shows a benefit of combining R with CHOP chemotherapy as either induction therapy or maintenance therapy but not both. Until recently, there were no Phase III data addressing the value of R in younger patients with DLCL-B. In the MInT Trial, evaluating R-CHOEP vs. CHOP in patients younger than age 60, patients received 6 cycles of any one of several CHOP-like regimens followed by radiation therapy (30–40 Gray to bulky disease or E lesions). The trial mixed early and advanced stage DLCL-B patients. Patients receiving R with chemotherapy had a significantly longer 2-year TTF (81% vs. 58%) compared with those receiving chemotherapy alone. In addition, the 2-year OS significantly favored chemotherapy plus R (95% vs. 85%, p = 0.0026). This trial did not deal with the poor-prognosis subset of younger patients. While dose-intensive regimens have shown some promising results they are clearly much more toxic and thus would need to be clearly superior to R-CHOEP before becoming standard therapy.

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11. 10 Years WHO Classification

WILL GENE EXPRESSION PROFILING REPLACE THE PATHOLOGIST?
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The completion of the first iteration of the human genome, together with significant advancements in nanotechnology and bioinformatics has resulted in a revolution in the way we think about and classify cancer. This has led to a paradigm shift for the classification of cancer, moving away from the traditional approaches of morphology and phenotype. Some texture to these new classifications will soon be added with the use of high-resolution cytogenetic studies and proteomics. Thus, molecular taxonomy for the classification of all cancers is a current reality.

Non-Hodgkin’s lymphomas (NHL) have proven themselves valuable candidates for these analysis techniques, allowing improved clarity of classification where there was heterogeneity, an example being the molecular definition of primary mediastinal large B cell lymphoma and its distinction from nodal DLBCL. Disease-specific classification gene lists exist as well as numerous genes that can be used to improved outcome prediction. The studies of NHL using genome-wide arrays have given way to the new era of customized, lymphoma-specific arrays (LymphRx), with both reduced RNA requirements and reduced cost. Both however, still require the need for frozen tissue, a resource that is not in plentiful supply. Moreover, GPB studies suffer from a number of vagaries, not the least of which is reproducibility. Comparability across GPB platforms continues to be a significant problem. Importantly, steady-state levels of mRNA are unlikely the sole mechanism controlling gene expression in neoplastic cells. Improvements in routine immunohistochemistry, the development of new monoclonal antibody reagents and efficient quantitative RT–PCR strategies are likely to gain more widespread use in the clinical translation of new knowledge acquired by GEP. This approach has already shown promise for the measurement of important biomarkers in NHL. In the future, genome-wide GEP techniques may be used to further define lymphoma biology and discover novel gene expression using small subsets of very well characterized NHLs, with more traditional strategies used in the clinic to complement existing diagnostic and prognostic approaches.

WHO-EORTC CLASSIFICATION FOR CUTANEOUS LYMPHOMAS
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Cutaneous lymphomas are nowadays classified according to the criteria of either the EORTC classification or WHO classification. Whereas there is consensus regarding most types of cutaneous T-cell lymphoma (CTCL), there has been an ongoing controversy on the classification of the different types of cutaneous B-cell lymphoma (CBCL) and the group of peripheral T-cell lymphomas (PTL), unspecified. Recently, intensive discussions between representatives of the EORTC and WHO groups resulted in a consensus classification: the WHO-EORTC classification for cutaneous lymphomas. Whereas many entities included in the original EORTC and WHO classification schemes remain unchanged, considerable progress was made with respect to the classification of the different groups of CBCL and of the group PTL, unspecified.

In the WHO-EORTC classification primary cutaneous follicle center lymphoma, including cases with a follicular (rare), a follicular and diffuse and a diffuse growth pattern, are included as a distinct entity. Primary cutaneous large B-cell lymphoma of the leg (PCLBCL-leg) was also acknowledged as a distinct disease entity. It was however also recognized that cases with a similar morphology (predominance of centroblasts and immunoblasts), phenotype (expression of bcl-2 and Mum-1) and prognoses may arise at other sites, and the term PCLBCL leg type is proposed for both cases arising on the legs and cases arising at other sites. From the group of PTL, unspecified aggressive CD8+ CTCL, cutaneous gamma/delta-T cell lymphomas (including subtypes: post-penile/penile-like T-cell lymphoma with a gamma/delta phenotype) and CD4+ small/middle-sized pleomorphic CTCL are recognized as provisional entities.

In this presentation differences between the EORTC classification and this new WHO-EORTC classification and their therapeutic consequences will be discussed. Clinical follow-up data of 1900 patients with a primary cutaneous lymphoma validating this new classification are presented. Moreover, the effects of recent molecular genetic studies on this and future classification schemes, which will increasingly incorporate genetic criteria, are discussed.

TYPING OF MATURE AGGRESSIVE B-NHLs IN THE CONTEXT OF THE WHO CLASSIFICATION BY A COMPREHENSIVE INTERDISCIPLINARY APPROACH USING GENOME-WIDE MOLECULAR TECHNIQUES
H. Stein
on behalf of the MMLN Network (German Cancer Aid), Institute of Pathology, Berlin, Germany

Introduction: Mature aggressive B-NHLs are a highly heterogeneous group of neoplasms. So far there is no consensus with which criteria this lymphoma group should be subclassified.

Methods: 140 cases of aggressive B-NHLs were studied by morphologic, immunophenotypic, molecular genetic and interphase FISH approaches as well as genome-wide gene expression profiling and high-resolution matrix CGH. Statistical learning methods were used to discover expression patterns related to entities, clinical prognosis and presence of genetic alterations. A molecular predictor of entities and survival was constructed and validated in an independent test set of 80 specimens.

Results: Two major groups of aggressive B-NHLs are defined by the presence or absence of a MYC breakpoint or a MYC-associated expression signature, which poorly reflect most morphologic WHO-subtypes. Subgrouping of MYC-break-negative lymphomas according to expression signatures and immunohistochemical classifiers for the GCB/ABC-types revealed inconsistent results. Genetic variables including presence of chromosomal aberrations are currently integrated to generate a multiclass predictive model of MYC-negative aggressive B-NHLs (abstract Hummel). Similarly, MYC-positive lymphomas constitute a heterogeneous disease group with regard to morphology, immunophenotype and genetic aberrations. Preliminary analyses combining all generated data support a model suggesting “classical sporadic Burkitt-lymphoma” to contain an IG-MYC fusion in a relatively stable chromosomal background (abstract Siebert).

Conclusions: DNA microarrays applied in combination with a high resolution matrix CGH and extensive FISH studies are suitable to formulate molecular classifiers for aggressive B-NHLs.

ARE CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) AND SMALL LYMPHOCYTIC LYMPHOMA (SLL) THE SAME DISEASE?
M. Keating, P. McLaughlin, A. Tsiambolidou, S. O’Brien

Both CLL and SLL are indolent B-lymphocyte neoplasms characterized by the accumulation of small B-lymphocytes. In the current World Health Organization’s classification of tumors, CLL and SLL are classified together (characterized by monomorphic small mature looking B-lymphocytes). The sites of involvement are common with the difference in CLL and SLL being the involvement of the bone marrow and peripheral blood circulating lymphocytes of > 10 x 10^9/L, which is mandatory for CLL. Both CLL and SLL show efficiency of the nodal architecture with pseudo follicles being characteristic. The cells also have similar morphology with coarse chromatin, a round nucleus and small nucleoli. Atypical forms of CLL, such as those with trisomy 12, show larger cells and prolymphocytes are occasionally scattered throughout the involved site. Paraimmunoblasts are also found. In both CLL and SLL, involvement of the spleen is prominent. The phenotype of the CLL and SLL cells is that they are mature B-lymphocytes with either IgM or IgD on the surface. The cells are CD5 and CD19 co-expressing with weak expression of CD20. CD23 is present and CD22 is weakly expressed. CyclinD1 and FMC7 are usually negative or weakly expressed. Differential diagnoses of CLL/SLL are mantle cell lymphomas (MCL) and marginal zone lymphomas (MZL) in its various manifestations. There is more information available on the Ig heavy and light chain gene rearrangements in SLL than in CLL. Cytogenetic abnormalities, when they have been studied have been similar in CLL. If the SLL, it appears that SLL is less frequently associated with autoimmune hemolytic anemia and other autoimmune manifestations and hypergammaglobulinemia is less prominent in SLL than CLL. Gene
expression profiles in SLL are similar to CLL and different from MCL and MZL. SLL cells commonly express the adhesive molecule CD18 (LFA1) whereas CLL cells are negative. This difference may explore the lack of circulating cells in SLL. The response rate to chemotherapy and Rituximab is similar in CLL and SLL. Analysis of the characteristics of CLL and SLL is being undertaken at MDACC. Analysis of the results of these findings will be presented.

LYMPHOPLASMACYTIC LYMPHOMA, WALDENSTROM’S MACROGLOBULINEMIA AND SPLENIC MARGINAL ZONE LYMPHOMA-ONE DISEASE

Steven P. Treon, on behalf of the Third International Workshop on Waldenstrom’s Macroglobulinemia Bing Center for Waldenstrom’s Macroglobulinemia, Dana Farber Cancer Institute, and Harvard Medical School, Boston, MA, USA

Waldenstrom’s macroglobulinemia (WM) is a distinct B-cell disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells, and demonstration of an IgM monoclonal gammopathy. This condition is considered to be lymphoplasmacytic lymphoma as defined by the REAL and WHO classification systems. Extranasal mucosa-associated lymphatic tissue (MALT) lymphoma, nodal marginal zone lymphoma (NMZL) and splenic marginal zone lymphoma (SMZL) are considered distinct entities, though possess overlapping features with WM, including an IgM monoclonal protein. As part of the 3rd International Workshop on WM, the features of WM, MALT, NMZL and SMZL were considered so as to clarify whether these entities represented a common disorder. The results of these studies are as follows:

The results of these ongoing studies suggest that WM manifests distinct genetic and molecular differences from MALT, NMZL, and SMZL.

<table>
<thead>
<tr>
<th>Entity</th>
<th>BM</th>
<th>LN/SM</th>
<th>EN</th>
<th>IgM</th>
<th>Morphology</th>
<th>Immuno-phenotypic differences</th>
<th>Cytogenetics/molecular studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>WM</td>
<td>100%</td>
<td>&lt;20%</td>
<td>Rare</td>
<td>100%</td>
<td>LPC, diffuse; intertrabecular pattern in BM</td>
<td>CD11c: 6%; CD25; 88%; CD103; 0% Bcl-2; 69%</td>
<td>del(6)(q21–23) 30–70% somatic V\textsubscript{H} mutated genes; no intrachromosomal and major isotype switching</td>
</tr>
<tr>
<td>MALT</td>
<td>20%</td>
<td>Varies</td>
<td>Common</td>
<td>[1]</td>
<td>NA</td>
<td>t(11;18)(q21q21); t(14;18)(q32;q21) V\textsubscript{H} studies show hypermutation.</td>
<td>t(11;18)(q21q21); t(14;18)(q32;q21) V\textsubscript{H} studies show hypermutation.</td>
</tr>
<tr>
<td>NMZL</td>
<td>45%</td>
<td>100%</td>
<td>Rare</td>
<td>30%</td>
<td>NA</td>
<td>t(11;18)(q21q21); t(14;18)(q32;q21) V\textsubscript{H} studies show hypermutation.</td>
<td>+3; 55%; +7; 35%; del 6q21–25 also observed.</td>
</tr>
<tr>
<td>SMZL</td>
<td>Common</td>
<td>Rare</td>
<td>Rare</td>
<td>45%</td>
<td>CD11c: 39%; CD25: 44%; CD103: 40%; Bcl-2: 0%</td>
<td>del(7)(q21) 19%; +3q 19%; +5q 10%/V\textsubscript{H} studies show mutated and unmutated genes.</td>
<td></td>
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</tbody>
</table>

MANTLE CELL LYMPHOMA: TURNING CYCLIN D1 ON AND OFF
E. Enver, H. Liu1, J. Wang, J. Huang, B. Churmara
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Translocations involving the immunoglobulin heavy chain gene locus (IgH) are common in B cell malignancies such as multiple myeloma (MM) and non-Hodgkin’s lymphoma (NHL). Cyclin D1 is deregulated in most patients with mantle cell lymphoma and 20–30% of patients with multiple myeloma. The cyclin D1 locus represents a model system to study the role of epigenetics in B cell malignancy. Cyclin D1 is known not to be expressed in normal lymphocytes, yet is deregulated by IgH translocations and insertions, frequently at long distances. Preliminary studies investigating the epigenetics of the cyclin D1 gene locus have revealed that the cyclin D1 locus, including the promoter and upstream regions are acetylated and DNA hypomethylated in non-malignant B cells. However, RNA polymerase II (Pol II) is only present at the promoter of cyclin D1 overexpressing cell lines. In addition, Pol II is located at regions far upstream of the cyclin D1 gene and at IgH regulatory elements. Utilizing genetic variants that have lost the translocated chromosome, we have shown that the translocated chromosome exerts a trans-hypomethylating effect on the normal chromosome (transvection). We have also demonstrated, using chromatin immunoprecipitation (ChIP) assays, the presence of the DNA binding protein CTCF and its partner nucleoplasmin (NPM) both at the cyclin D1 promoter and IgH regulatory regions only in cyclin D1 overexpressing cell lines. Fish/Hc studies have shown that cyclin D1 loci at the nucleolar membrane in MCL cells. Using RNA interference (RNAi) studies we have shown that NPM RNAi severely and specifically inhibits the growth of MCL cell lines and dramatically reduces cyclin D1 protein levels. We propose CTCF and nucleoplasmin play a critical role in deregulated expression of cyclin D1 in MCL by tethering the 3′ regulatory regions to the cyclin D1 promoter at the nucleolar membrane. More recently, we have obtained additional evidence that NPM is critical in other hematologic malignancies that contain chromosomal translocations such as Burkitt’s lymphomaa and CML.

We are also studying novel therapeutic agents in vitro and in vivo for mantle cell lymphoma. The first class of agents are capable of downregulating cyclin D1 RNA or protein. Iron chelating agents such as deferasirox downregulate cyclin D1 mRNA while velcade and curcumin downregulate cyclin D1 protein in MCL cell lines in vitro. Novel therapies targeted against NPM in vitro and in vivo are also being developed.

MANTLE CELL LYMPHOMA (MCL): WHAT’S NEW?
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MCL accounts for approximately 6–7% of all NHLs and typically carries a dismal prognosis, with median overall survival of approximately 3 years. The majority of cases can now be accurately diagnosed using improved, paraffin-active cyclin D1 monoclonal antibodies. Together with anti-CD5 antibodies and locus-specific FISH techniques, the full morphological spectrum of MCL can now be readily appreciated, including classical, blastoid and pleomorphic histologic variants. Similarly, there exists a clinical spectrum of behavior in MCL, with small numbers of patients enjoying lengthy survival. Some data suggests that these cases may be associated with somatic mutation of the IgH locus, indicative of transit through the germinal center.

Typically the more aggressive appearing blastoid cases are associated with recognized molecular alterations that are themselves associated with inferior survival, including a tetraploid karyotype, p53 mutations, p16 loss and an elevated proliferation fraction. Gene expression profiling (GEP) studies have recently demonstrated the prognostic importance of the proliferation signature, which contributes a dominant effect on survival in MCL. Both p53 mutation and p16 gene loss predict survival in MCL, but are affected by the effect of increased proliferation. Several of these features, together with new findings related to alternative cyclin D1 transcription variants will be discussed.

The cyogenetic hallmark of MCL is the t(11;14)(q13;q32), leading to deregulated cyclin D1 production. Most cases demonstrate a number of secondary genetic alterations that are likely important contributors to pathogenesis. The clarity of these molecular changes has been improved following the use of techniques such as chromosomal comparative genomic hybridization (CGH) and significantly enhanced using high-resolution array-based CGH techniques. Together with proteomic analyses, these approaches to studying lymphoid tumors should provide insight into novel mechanisms of deregulated gene expression in MCL and perhaps help to identify the next set of therapeutic targets.

CURRENT STRATEGIES IN MANTLE CELL LYMPHOMA: CONVENTIONAL THERAPY
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Introduction: Mantle cell lymphoma (MCL) is a distinct subtype of malignant lymphoma which is characterized by the chromosomal translocation t(11;14)(q13;q32) resulting in constitutional overexpression of cyclin D1 and cell cycle dysregulation in virtually all cases. MCL shows an aggressive clinical course with a continuous relapse pattern and a median survival of only 3–4 years. Advanced stage disease is usually apparent already at first clinical manifestation; thus, conventional chemotherapy only is palliative and median duration of remissions is only 1–2 years.

Induction: In the only prospective randomized study, an anthracycline containing regimen (CHOP) was not superior to another combination (COP). In contrast, retrospective surveys suggest that MCL patients with low risk profile may benefit from the addition of anthracyclines. Although purine analogs like Fludarabine have only a moderate activity in monotherapy (remission rates of 30–40%), combinations with alkylators (e.g. cyclophosphamide +/− mitoxantrone) achieved significantly higher CR and overall response rates of 30% and >60%, respectively, in relapsed MCL (70% CR in first line therapy). Another promising approach is the application of high dose ara-C which achieved remarkable response rates. In a phase II study of a sequential CHOP/DHAP regimen, CR rate was only 7% after 4 cycles of CHOP; this CR rate was increased to >80% after 4 additional cycles of DHAP. Similarly, in a monocentric study at MD Anderson, a dose-intensified induction (Hyper-CVAD) achieved a 92% remission rate in elderly patients.

The anti-CD20 antibody Rituximab has only moderate activity in monotherapy of MCL (response rates of 20–35%). However, in two randomized studies the superiority of a combined immuno-chemotherapy could be confirmed. In first line therapy (R-CHOP vs. CHOP: OR/CR 94%/54% vs. 75%/27%; P = 0.005) as well as relapsed MCL (R-FCM vs. FCM: OR/CR: 88%/29% vs. 46%/0%; P = 0.003), the addition of Rituximab resulted in a significant increase of CR and overall response rates.

Consolidation: Median duration of remission after induction alone is rather short (12–30 months). In two phase III studies, interferon maintenance resulted in a slightly improved progression-free survival, but this difference was not statistically significant due to the small patient number, and continuous relapses have been observed. Radioimmunotherapy with either 131I-Idone or 131I-Yttrium labelled antibodies may represent another promising therapeutic option which is currently evaluated in clinical studies.

HIGH DOSE THERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION IN MANTLE CELL LYMPHOMA
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Mantle cell lymphoma (MCL) is characterized by a poor prognosis with a median survival of only 3–4 years. To improve clinical outcome several groups have investigated myeloablative therapy followed by autologous stem cell transplantation (ASCT) as consolidation and useful transplantation procedure. In first or subsequent remission. In patients being transplanted in >1 remission, duration of remission was mostly short with less than 30% of patients remaining disease free at two years.
More encouraging data emerged from the application of ASCT in 1st remission. In several phase II studies ongoing remissions were reported in the range of 50–70% at two or three years. The European MCL Network completed the only currently available prospective randomized trial comparing ASCT with IFNα maintenance in 1st remission in patients up to 65 years of age with advanced stage MCL. With 122 evaluable patients ASCT resulted in a significantly longer duration of remission with a median of 39 months as compared to 17 months for patients in the IFNα arm (P=0.0108). The three year overall survival (OS) was 83% in the ASCT arm vs. 77% in the IFN group (P =0.18). However, after ASCT relapses were ongoing and no long term plateau was achieved. Hence, although ASCT certainly represents a highly effective therapeutic modality additional measures such as more effective initial cytoreductive chemotherapy and/or improved in vivo purging with monoclonal antibodies are required to further improve the outcome of MCL patients.

NEW TREATMENTS FOR MANTLE CELL LYMPHOMA

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Mantle cell lymphoma (MCL) responds to chemotherapy but responses are generally temporary and the disease is usually incurable. Depending upon the clinical circumstance, treatment strategies range from observation to aggressive treatment. A variety of treatment strategies are under investigation. Aggressive chemotherapy-immunotherapy such as Hyper-CVAD-rituximab has yielded promising results in younger patients. Its curative potential, however, requires longer follow-up. Less aggressive chemotherapy platforms such as CHOP or FCM with rituximab have high response rates but of limited duration. Strategies such as maintenance rituximab have not demonstrated survival benefit in mantle cell. Radioimmunoconjugates have demonstrated activity in relapsed mantle cell lymphoma and are under investigation in untreated patients. Immunotherapy with allogeneic transplant have yielded promising early results and suggest the presence of a graft-versus-mantle cell effect. Other immune approaches such as idotype vaccine, however, have been less promising. Small targeted agents have shown promise. Bortezomib, a proteasome inhibitor has produced upwards of 50% response rates in previously treated mantle cell lymphoma in two small phase II studies. Based on such results, studies are planned to investigate the role of bortezomib with chemotherapy in untreated mantle cell and the role of maintenance bortezomib. Other novel small molecules which require investigation in mantle cell lymphoma include histone deacetylase (HDAC) inhibitors, and suberoylanilide hydroxamic acid (SAHA), which down regulates cyclin D1 and other cell cycle specific proteins. Anti-angiogenesis agents, such as thalidomide, in combination with rituximab have shown promise. Other immuno-modulatory (IMIDs) agents are also important candidates for investigation.