MOLECULAR PATHOGENESIS OF DIFFUSE LARGE B CELL LYMPHOMA

R. Dalla-Favera
Institute for Cancer Genetics, Columbia University, New York, NY, USA

Diffuse large B cell lymphomas (DLBCLs) are biologically and clinically heterogeneous tumors that arise by malignant transformation of germinal center (GC) B cells, a process that entails the accumulation of multiple lesions in specific proto-oncogenes and tumor suppressor genes. These genes are altered by mechanisms common to other cancer types, such as gene amplification and deletion, as well as by two mechanisms that involve errors in genetic functions specific to GC B cells: i) chromosomal translocations that lead to deregulated expression of oncogenes (BCL2, BCL6, c-MYC) and are thought to represent mistakes of Immunoglobulin (Ig) Class Switch Recombination (CSR); and ii) aberrant somatic hypermutation (ASHM), which causes mutations in the 5' region of multiple oncogenes and is due to the malfunction of a process, somatic hypermutation (SHM), that normally acts on Ig genes to allow antibody affinity maturation (Pasqualucci et al., Nature, 2001). The variable combination of genetic lesions caused by these mechanisms may be the basis for the unusual heterogeneity of DLBCL. One common pathogenetic target is the BCL6 proto-oncogene, which encodes a transcriptional repressor necessary for GC formation (Ye et al., Nature Genetics, 1998), and whose expression is frequently deregulated in DLBCLs by chromosomal translocation or SHM (Ye et al. Science, 1994; Pasqualucci et al., Blood, 2004). One major function of BCL6 is to suppress p53 expression during the GC reaction, possibly to allow execution of the physiologic genomic break/recombination events required for CSR and SHM without eliciting a p53-mediated apoptotic response (Phan and Dalla-Favera, Nature, 2004). Recent studies suggest that multiple cellular pathways inversely regulate the expression of BCL6 and the apoptotic responses to genotoxic stress. As such, DLBCL cells that constitutively express BCL6 may be functionally impaired in both p53-dependent and p53-independent cell cycle arrest and apoptotic responses. These mechanisms and their therapeutic implications are being validated in a mouse model of DLBCL generated by deregulating BCL6 expression in GC B cells (Cattoretti et al., Cancer Cell, 2005).
OPTIMISATION OF BEACOPP FOR ADVANCED HODGKIN'S DISEASE: FINAL RESULTS FROM GERMAN HODGKIN STUDY GROUP TRIALS HD9 AND HD12
V. Diehl1, C. Brillant1, J. Franklin1, A. Engert1, B. Pfistner2, R. Greil3, R. Herrmann3
1GHSG, University Hospital Cologne, Köln, Germany; 2AGMT, St. Johannes Spital, Salzburg, Austria; 3SAXK, Kantons spitäl, Basel, Switzerland

Introduction: Dose-escalated BEACOPP proved more effective than conventional COPP/ABVD in HD9. In HD12 we tested a dose-reduced variant to reduce toxicity. Here we assess long-term survival and second leukemias (SL) with BEACOPP and the effectiveness of the reduced-dose regimen with/without radiotherapy.

Methods: HD9: In 1993–98, 1201 patients aged 16–65, stage IIIA or IIA with risk factors or stage IIIB–IV were randomised to 4x(COPP + ABVD) (4C), 8x baseline BEACOPP (8B) or 8x escalated BEACOPP (SE), with radiation of initial bulky and residual disease (BR-RT). HD12: In 1999–2002, 1396 patients aged 16–65 in stage IIB with risk factors or stage III–IV were randomised in a factorial design to SE (arms A, B) vs. 4x escalated plus 4x baseline BEACOPP (4E4B) (arms C, D), and then randomised to BR-RT (arms A, C) vs. no irradiation (B, D). An expert panel reviewed results after chemotherapy and advised on radiation independent of arm.

Results: With 82 months median follow-up in this update to HD9, the estimated FTPF and OS rates were: 4C: 67% and 79%, 8B 75% and 84%, SE 85% and 90% (p less than 0.001 and P<0.004) respectively. In HD12, 61 second malignancies were documented, similar in each arm. More SL occurred with SE (11/466) than 8B (5/469) or 4C (1/260). In the 4th interim analysis of HD12 with 30 months median follow-up, FTPF rate was 88% (95%-CI 86–90) and OS rate 94% (92–95) for the total cohort. Radiation was given in arms A+C in 66% and in arms B+D in 9% (mostly panel recommendation). There were 29 second malignancies; the rate of SL (11/1396) at this early analysis was lower than in HD9. Group sequential analysis showed no significant arm differences.

Conclusions: Escalated BEACOPP increases second leukemia risk, but does not yield overall survival superior to COPP/ABVD or baseline BEACOPP. 4E4B appears to be equivalent to 8E, but longer follow-up is needed. Progress of the current trial HD15 investigating alternative reductions of BEACOPP will also be reported.

A RANDOMISED CONTROLLED TRIAL OF ABVD VS TWO MULTI-DRUG REGIMENS FOR ADVANCED HODGKIN Lymphoma - Updated Results of UKLG LY09
J. A. Radford1, M. H. Callen2, B. W. Hancock3, J. Walewska4, M. R. Sydes5, D. Ryder2, P. Smith1, S. Clawson6, S. P. Steenings7, P. W. M. Johnson8. On behalf of all the collaborators of the trial. 1Medical Oncology, Christie Hospital NHS Trust, Manchester, UK; 2Queen Elizabeth Hospital, Birmingham, UK; 3Clinical Oncology, University of Sheffield, Sheffield, UK; 4MCCM Cancer Centre, Warsaw, Poland; 5London, UK; 6Medical Oncology Unit, Southampton General Hospital, Southampton, UK

Introduction: This international randomised controlled trial, organised by the UK Lymphoma Group (UKLG), compared ABVD with two multi-drug regimens (MDR) for the treatment of advanced Hodgkin Lymphoma (HL) in terms of progression-free survival (PFS) and overall survival (OS).

Methods: Patients with advanced HL (stage IIIC–IV) were randomised between standard therapy with ABVD and one of two MDRs: Alternating CHVPP/PABIOE or Hybrid CHVPP/EVA. Six cycles were planned, plus two extra for slow responders, with radiotherapy planned for incomplete response or poor bulk. MDR choice was specified at randomisation; patients were effectively randomised between ABVD and Alternating or between ABVD and Hybrid.

Results: 807 patients were randomised between April 1997 and September 2001; 406 allocated ABVD and 401 MDRs. The groups were well-balanced: 45% female, mean age 47 years, 36% ECOG score 0–1. Chemotherapy administration: doxorubicin Dose Intensity was >=80% planned for 81% of patients allocated ABVD, 90% Alternating and 86% Hybrid. 40% of patients received radiotherapy at the completion of chemotherapy. At 3 years median follow-up, 193 PFS events were reported. For the primary ABVD vs MDR comparison, PFS hazard ratio (HR) = 1.04, 95% CI (0.79, 1.39), P = 0.58 (HR > 1.0 favours ABVD) with no clear evidence of heterogeneity according to choice of MDR (x2 = 0.30). The survival HR = 1.16 (0.78, 1.74), P = 0.46 with 3-year survival rates of 91% and 90% for ABVD and MDR respectively.

Conclusion: No clear evidence of a difference between ABVD and the MDRs was demonstrated with respect to PFS and OS. A centre effect was evident in the duration of chemotherapy and use of radiotherapy; this was related to the pre-randomisation choice of MDR but was balanced across the allocated treatment arms. (Final results will be presented).

RADIATION DOSE IN NON-HODGKIN'S LYMPHOMA: PRELIMINARY RESULTS OF UK NCNR RANDOMISED TRIAL
P. Hoskin et al. Centre for Cancer Treatment, Mount Vernon Hospital, UK

Introduction: Radiotherapy is widely used in the management of non-Hodgkin’s lymphoma (NHL) but the optimal dose to control NHL has not been established. Standard practice in the UK is to deliver doses of 35 to 40 Gy with no distinction between different histological types. A randomised trial of radiation dose in NHL has been undertaken to compare a conventional dose of 40 Gy with lower doses of 30 Gy in high grade and 24 Gy in low grade NHL.

Methods: All patients receiving local radiotherapy for local control of lymphoma who received chemoradiotherapy as radical treatment of stage I disease, consolidation therapy after chemotherapy or palliation of advanced disease were eligible. Patients with low grade NHL (LG) were randomised to receive 24 Gy in 12 fractions daily or 40–45 Gy in 20–23 fractions daily. Patients with intermediate or high grade lymphoma (IHG) were to receive 30 Gy in 15 fractions daily or 40–45 Gy in 20–23 fractions daily. The trial started before the WHO histological classification: low grade comprised follicular lymphoma (excluding large cell type) and diffuse small lymphocytic lymphoma; other histological types being randomised in the intermediate/high grade stratification. The primary end point was local control (one month after the completion of the radiotherapy) in the irradiated volume; secondary end points included acute toxicity.

Results: Between April 1997 to January 2005, 1000 patients were randomised (359 LG, 641 IHG). Patients characteristics between low and high dose radiotherapy were well balanced in both LG and IHG groups: median age of 63, 50% male and 93% stage I at diagnosis in the LG group; median age of 65, 54% male and 56% stage I in the IHG group. 95% patients received protocol treatment dose. Indications for radiotherapy were radical (78%), palliative (16%) and consolidation (6%) in the LG group, and 49%, 6% 45% respectively in the IHG group. Acute reactions did not differ between the two groups. The trial was closed on 31 January 2005, updated results will be presented at the meeting.

Conclusions: Local radiotherapy is highly effective at achieving local control of NHL with no clear advantage emerging so far for doses higher than 24 Gy in low grade and 30 Gy in intermediate/high grade disease.

RITUXIMAB PLUS MITOXANTRONE, CHLORAMBUCIL, PREDNISOLON (R-MCP) IS SUPERIOR TO MCP ALONE IN ADVANCED ENDOLymphATIC AND FOLLICULAR LYMPHOMA – RESULTS OF A PHASE III STUDY (OSHO39)
1HämatoLOGikOnkologie, HELIOS Klinikum Erfurt, 2Medizinische Klinik, Erfurt, Germany; 3for the East German Study Group, HématoLOGikOnkologie (OSHO), Leipzig, Germany

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Introduction: Rituximab proved to be effective in relapsed and refractory indolent NHL as a single agent and generated impressive results in combination with chemotherapy in phase II and more recently also in first line phase III studies.

Methods: In a prospective randomised trial we compared the efficacy and toxicity of rituximab (375 mg/m² d 1) plus MCP-chemotherapy (mitoxantrone 8 mg/m² d 3+4, chlorambucil 3 x 3 mg/m² d 3–7, prednisolone 25 mg/m² d 3–7) given q 4 weeks x 8 versus MCP alone q 4 weeks x 8 in advanced follicular lymphoma, immunocytoma and mantle cell lymphoma. Study end points included overall and complete response rate, progression free survival, event free survival, overall survival and toxicity.

Results: From 1098 to 9/03 we randomized 374 patients of which 358 are evaluable on an intention to treat basis, among these 201 with follicular lymphoma (FL) (R-MCP 105; MCP 96), the main focus of the study. Concerning this subgroup the results are as follows (median follow up 30 months):

<table>
<thead>
<tr>
<th>R-MCP (%)</th>
<th>MCP (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>92.4</td>
<td>75</td>
</tr>
<tr>
<td>Complete response</td>
<td>49.5</td>
<td>25</td>
</tr>
<tr>
<td>PFS (30mon.)</td>
<td>82.2</td>
<td>50.7</td>
</tr>
<tr>
<td>EFS (30mon.)</td>
<td>79.3</td>
<td>44.4</td>
</tr>
<tr>
<td>OS (30mon.)</td>
<td>89.3</td>
<td>75.5</td>
</tr>
</tbody>
</table>

Both regimens were well tolerated with a low incidence of serious adverse events.

Conclusions: Concerning all end points R-MCP is significantly superior to MCP and this is the first phase III study in the first line treatment of advanced follicular lymphoma to demonstrate a significant survival advantage for immunochemotherapy over chemotherapy alone.

THE ROLE OF RITUXIMAB MAINTENANCE TREATMENT IN RELAPSED FOLLICULAR NHL: AN INTERIM ANALYSIS OF THE EORTC RANDOMIZED INTERGROUP TRIAL

A. Huguenin-Beck1, M. Van Glabbeek2, J. Teodorovic2, C. Rozewicz2, R. Kluss1, R. E. Marcus1, M. Wolf1, E. Kimby3, M.H.J. van Oers1,2
1EORTC Lymphoma Group, University Medical Center Utrecht, Utrecht, Netherlands; 2EORTC, Centre for Clinical Research, Brussels, Belgium; 3NCI, CTG Hematology Group, Vancouver, Canada; BNLL, Cambridge, UK; 4Australian Leukemia, and Lymphoma Group, Melbourne, Australia; 5Nordic Lymphoma Group, Stockholm, Sweden; HOVON, Utrecht/Amsterdam, Netherlands

Introduction: Results are presented of a phase III clinical trial in patients with relapsed/refractory follicular NHL comparing, firstly, CHOP with Rituximab + CHOP (R-CHOP) induction and, secondly, maintenance treatment with Rituximab in responding patients.

Methods: Patients were randomised between 6 cycles of CHOP vs 6 cycles of R-CHOP. Responding patients underwent a second randomization between observation vs R-maintenance (375mg/m² every 3 months until relapse or for a maximum period of two years).

Results: 461 patients were included, of which 369 were evaluable for response. CR: CHOP 18.1% vs R-CHOP 30.4% (P=0.0004); PR: CHOP 53.7% vs R-CHOP 52.5% (ns); PFS at a median follow-up of 26 months: CHOP 20 mths vs R-CHOP 30 mths (P=0.0007). 319 patients were randomized to maintenance treatment. PFS at 3 yrs: observation 31.2% vs R-maintenance 67.7% (P<0.0001). The observed difference in OS in favour of R-maintenance was considered not significant for an interim analysis (P=0.03). No differences in toxicity were observed between the arms. With these results the primary endpoints for both the induction and maintenance part of the study had been reached, and the formal criteria for stopping the trial were met.

Conclusions: In patients with relapsed/resistant follicular lymphoma R-CHOP remission induction results in a highly significant increase in CR rate as compared to CHOP. Moreover, this is the first trial to show that in these patients Rituximab maintenance treatment achieves a considerable improvement in PFS.

FLIPI PREDICTS OUTCOME IN 65 PATIENTS WITH PREVIOUSLY UNTREATED INDOLENT NHL WHO RECEIVED BEXAR® IN COMBINATION WITH CHEMOTHERAPY

J. Leonard
Center for Lymphoma and Myeloma, Weill Medical College of Cornell University and New York Presbyterian Hospital, New York, NY, USA

Background: Tositumomab and iodine 131 Tositumomab (the BEXAR® Therapeutic Regimen, hereafter iodine 131 Tositumomab) yields high rates of durable and complete (CR) responses in pts with previously untreated indolent non-Hodgkin’s lymphoma (NHL).

Methods: The efficacy, including the prognostic value of the follicular lymphoma international prognostic index (FLIPI) and the safety of this regimen were reviewed for 65 pts with previously untreated indolent NHL in 2 studies: 35 pts receiving an abbreviated regimen of 3 cycles of fludarabine followed by iodine 131 Tositumomab, and 30 pts receiving 6 courses of CVP followed by iodine 131 Tositumomab. Investigator efficacy assessments were used. Median follow-up was 52 mo (range 16–73).

Results: Median age: 51 yr (range 25–82 yr); median time from NHL dx: 3 mo; stage III/IV: 97%; tumor diameter 25 cm: 55%; bone marrow involvement: 67%. Overall response rate was 100% (95% CI 94%, 100%); CR rate was 88% (95% CI 77%, 94%). Median progression-free survival (PFS) was not reached. The 5-year PFS was 57% (95% CI 45%–72%). In univariate analyses, age patient 60, elevated LDH, hemoglobin<12 g/dL, and FLIPI were significant predictors of PFS. The 5-year PFS were 76%, 71%, and 33% for low-risk, intermediate-risk, and high-risk FLIPI groups, respectively (P<0.002, log-rank test). In multivariate analyses, high-risk FLIPI score was the only significant predictor of PFS (P<0.001). Intuions were well tolerated (rate adjustments in only 5% of infusions).
of patients received supportive care following Iodine I 131 Tositumomab. Overall only 6% of pts had a drug-related serious AE after Iodine I 131 Tositumomab. Elevated HAMA levels occurred in 3% of pts.

**Conclusions:** Iodine I 131 Tositumomab in combination with chemotherapy was well tolerated and resulted in prolonged PFS in pts with previously untreated LG NHL. The FLIPI score was identified as the factor most prognostic of PFS.
15. Clinical Results in Lymphoma II

SEQUENTIAL RADIOIMMUNOTHERAPY WITH TOSITUMOMAB-BIODINE 1113 TOSITUMOMAB FOLLOWED BY CHOP CHEMOTHERAPY FOR MANTLE CELL LYMPHOMA IS A SAFE AND HIGHLY EFFECTIVE REGIMEN

A. Zelemenga, G. Donnelly, N. Pandit-Taskar, J. Humm, C. Divgi
Lymphoma and Nuclear Medicine Services, Memorial Sloan-Kettering Cancer Center, New York, USA

We have investigated a sequential regimen of radioimmunotherapy (RIT) with tositumomab/biodine 1113 tositumomab (BEXXAR) followed 12–15 weeks later by CHOP chemotherapy for the treatment of patients with newly diagnosed MCL. Patients had to either be ineligible for or refuse high dose therapy and stem cell transplant (HD SCT) to be eligible for this therapy. In addition, they had to have less than 25% of the intraradicular space of the bone marrow involved by MCL. Patients had to have adequate renal function and at least 100,000 platelets per microliter. All patients underwent pre-treatment evaluation with colonoscopy to evaluate the extent of GI tract involvement. The study has completed accrual with 25 patients, 24 of whom were treated. The median age was 66 (range 45–80). There were 23 men and 2 women. All patients had advanced stage disease (CS III 4; CS IV 21). Bone marrow was involved in 48% and the GI tract in 48%. All of the 24 treated patients are evaluable for response to the RIT. The overall response rate to RIT was 83% (CR/Cru 10; 42%; PR 10, 42%). Two patients withdrew consent after the RIT and 1 patient had progression requiring alternative therapy. Sixteen patients are evaluable at the end of therapy response (including the patient with PD after RIT) with an OR in 14/16, 88% (CR/Cru 12, 75%; PR 2, 13%). 1 patient died of a CVA during the CHOP chemotherapy and 5 patients have not completed the chemotherapy phase of the regimen. The fifteen patients who completed therapy have been followed for 2–36 months; 9 patients remain in an unmaintained remission. Two patients who had initially refused HD SCT received this therapy on progression and tolerated it well. The toxicity of the regimen was predictable and manageable, details will be presented. This study demonstrates that RIT has substantial single agent activity in MCL and that sequential RIT and chemotherapy is both feasible and effective with manageable toxicity even in elderly patients. This regimen can serve as a platform for evaluation of post remission therapy which will be necessary to prevent relapse.

YTTRIUM-90 Ibritumomab Tiuxetan (Zevalin) INDUCES HIGH RESPONSE RATES IN PREVIOUSLY TREATED PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA (DLBCL)

E. Morschhauser1, D. Hugo2, G. Martellini3, G. Paganeli4, P. Zinzani2, D. Hadiyianakisa, A. Liberati1, T. Illigde5, N. Milpied2, J. Kalmus6, P. Morel7, U. Reimann6, R. Marcus1

1Hematology, CHRU, Lille, France; 2Nuclear Medicine, CHRU, Lille, France; 3Oncology, Hematology, European Institute of Oncology, Milano, Italy; 4Nuclear Medicine, European Institute of Oncology, Milano, Italy; 5Hematology, University of Bologna, Bologna, Italy; 6Oncology, Derriford Hospital, Plymouth, UK; 7Internal Medicine, Policlinico Monteluce, Perugia, Italy; 8Oncology, CRUK Patterson Institute and Christie Hospital, Manchester, UK; 9Hematology, CHRU, Nantes, France; 10Clinical Development Oncology, Schering AG, Berlin, Germany; 11Haematology, Addenbrooke’s Hospital, Cambridge, UK

Yttrium-90 (90Y) ibritumomab tiuxetan is highly active in patients (pts) with follicular lymphoma. We conducted an open-label, multicenter phase II trial to evaluate the efficacy and safety of 90Y ibritumomab tiuxetan in elderly pts with relapsed/refractory DLBCL not appropriate for autologous stem cell transplantation (ASCT). Pts previously treated with chemotherapy alone [A, n=76], or chemotherapy + rituximab [B, n=28] were included. The chemotherapy group was divided into those with primary refractory disease [A1, n=33], relapsed 1 year from presentation [A3, n=33]. A total of 100 pts were evaluable for efficacy and received a single 14.8 MBq Kg (0.4 mCi/Kg) dose of 90Y ibritumomab tiuxetan up to a maximum of 1184 MBq (32nCi). Endpoints included overall response rate (ORR), progression-free survival, overall survival, and safety. ORRs ranged from 19%-58%, with CR/Cru rates of 11-45%. The current median follow-up is 18 months, and ~40% of all patients, including those who were refractory to their prior therapy, had a durable response. Median survival has not been reached in strata A1 and A2, and was 26.0 months in stratum A3 and 4.6 months in group B. The most common CTCAE grade 3/4 toxicities were thrombocytopenia and neutropenia. Four deaths occurred; 3 of suspected cerebral hemorrhage preceded by CT grade 4 thrombocytopenia, 1 of bleeding from a duodenal ulcer which was deemed not related to the study drug. The incidence of severe infection was low; only 7% of patients were hospitalized for infection during the study. 90Y ibritumomab tiuxetan induced high and durable response rates in previously treated pts with DLBCL. Treatment with 90Y ibritumomab tiuxetan was well tolerated, with no unexpected toxicities observed. Further evaluation of 90Y ibritumomab tiuxetan as part of first-line therapy in DLBCL is now justified.

AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) AS CONSOLIDATION CHEMOTHERAPY (CT) FOR PATIENTS (PTS) WITH LOW-INTERMEDIATE (LI) RISK DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) AND OVEREXPRESSION OF BCL2 PROTEIN. RESULTS OF THE GELA TRIAL LN98-82

P. Morel1, N. Mounier2, J. Brie3, O. Herment1, C. Ferme1, B. Coiffier2, H. Tilly1, P. Gaulard1, P. Leclerc4, F. Reves1, C. Gisselbrecht2

1Hematologie, Hopital Schaffner, Lens, France; 2Hematologie, Centre Claudine, Grenoble, France; 3Hematologie, Centre Claudine, Grenoble, France; 4Hematologie, Centre Claudine, Grenoble, France

Introduction: Up to 32% of pts aged ≤60 years (ys) are at LI-risk. In a previous trial specifically designed for these pts, DLBCL pts achieved a 5-y EFS at 68% after ACVBP, with a lower 2-y EFS in pts with bcl-2 overexpression (71% vs. 82%, P=0.04). In order to reduce treatment failure in bcl-2 positive pts, we initiated a trial stratified by bcl-2 expression.

Methods: Centralized staining for bcl-2 was obtained within 6 weeks after inclusion. Induction CT consisted of 4 courses of ACVBp given every 2 weeks. In case of response, bcl-2 negative pts received the conventional consolidation CT, whereas bcl-2 positive pts received a second peripheral blood stem cell collection after the 4th cycle, and ASCT (mitoxantrone 45 mg/m2, cyclophosphamide 1.5 g/m2x4d, etoposide 250 mg/m2x4d and Carmustine 300 mg/m2) within 90 days.

Results: From 1999 to 05/2003, 316 LI-risk pts aged 18 to 59 (median 46, M/F=1.3) presented with bcl-2 overexpression (177) and without (139). There was no difference in toxicity of induction CT and complete response (CR + CRu) rates between bcl-2 positive and bcl-2 negative pts (79% and 81%, respectively). ASCT was not performed in 40 pts, mainly because of early failure (30%), or toxicity after induction (24%). Two-year overall survival was estimated 89% with a median follow-up of 29 months. Although bcl-2 negative pts retained a better 2-y survival than bcl-2 positive pts (96% vs. 84%, P=0.002), 2-y EFS and 2-y DFS did not differ significantly (81% vs. 78%, P=0.27, and 84% vs. 83%, P=0.56 respectively).

Conclusions: The 2-y survival rate achieved by this risk-adapted strategy compares favorably with other treatment approaches. The lack of difference in EFS and DFS between bcl-2 positive pts who received ASCT and bcl-2 negative pts suggested that ASCT may overcome the adverse prognostic value of bcl-2 overexpression in LI-risk pts who achieve CR or CRu.

DOSE-ESCALATED CHOP PLUS ETOPOSIDE (MEGACHOP) FOLLOWED BY REPEATED TRANSPLANTATION OF AUTOLOGOUS PERIPHERAL BLOOD STEM CELLS (PBSC) IN YOUNGER PATIENTS WITH AGGRESSIVE NHL – A SERIES OF PHASE II STUDIES BY THE GERMAN HIGH-GRADE NHL STUDY GROUP (DSHNHL)

N. Schmitz1, K. Marisa2, A. Engert1, W. Berdel1, B. Mezies3, L. Trümper1, M. Löffler1, M. Pfreundschuh2, B. Glass3

1Hämatologie, AK St. Georg Hamburg, Hamburg, Germany; 2IMISE, UK London, Leipzig, Germany; 3Medizinische Klinik I, UK Köln, Köln, Germany; 4Medizinische Klinik A, UK Münster, Münster, Germany; 5Abteilung Hämatologie und Onkologie, Städt. Klinik Oldenburg, Oldenburg, Germany; 6Abteilung Hämatologie und Onkologie, UK Göttingen, Göttingen, Germany

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Introduction: The role of high-dose therapy (HDT) followed by PBSC/T in primary treatment of younger pts (<60 years) with aggressive lymphoma remains controversial.

Methods: We embarked on a series of phase II studies characterized by 1. dose escalation of drugs with known activity in high-grade NHL (CHO-P + etoposide) 2. administration of 4 to 6 treatment courses to achieve high doses and dose intensities. 3. addition of Rituximab (R). Doses of ADRI, VCR, and PRD were identical at all dose levels (DL). Cumulative doses of CY and ETO were: DL1: CY 16.5 g/m², ETO 2.5 g/m²; DL2: CY 16.5 g/m², ETO 4.0 g/m²; DL3 CY 19.5 g/m², ETO 5.04 g/m². At DL3, pts were randomized between 4 or 6 courses, at all other DL 4 courses were given. PBSC/T was performed after the last 3 courses of treatment.

Results: 312 pts were treated with the following results:

<table>
<thead>
<tr>
<th>Therapy</th>
<th>n</th>
<th>Duration of therapy (mo.)</th>
<th>CR (%)</th>
<th>TTF (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DL 1+2</td>
<td>110</td>
<td>85 30</td>
<td>74</td>
<td>67</td>
<td>75</td>
</tr>
<tr>
<td>DL 3/4</td>
<td>42</td>
<td>99 29</td>
<td>68</td>
<td>53</td>
<td>70</td>
</tr>
<tr>
<td>DL 3/6</td>
<td>26</td>
<td>142 38</td>
<td>50</td>
<td>23</td>
<td>46</td>
</tr>
<tr>
<td>DL 3+ R</td>
<td>72</td>
<td>99 18</td>
<td>76</td>
<td>70</td>
<td>74</td>
</tr>
</tbody>
</table>

Conclusions: Treatment results show excellent TTF and OS for young high-risk pts with aggressive NHL treated with MegaCHOEP. Importantly, higher doses of active drugs (CY, ETO) failed to improve outcome if given over prolonged periods of time resulting in loss of early dose intensity (DL 3/6).

HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL SUPPORT DOES NOT IMPROVE OUTCOME IN THE FIRST-LINE TREATMENT OF AGGRESSIVE NON-HODGKIN LYMPHOMA—RESULTS OF A COMPREHENSIVE META-ANALYSIS

A. Greb1, J. Bohlke1, G. Schwarzer2, D. Schiefer1, A. Engert1
1German Cochrane Center, Institute of Medical Biometry and Medical Informatics, Freiburg, Germany; 2Department I Internal Medicine, Cochrane Haematological Malignancies Group, University of Cologne, Cologne, Germany

Background: Randomized controlled trials (RCTs) reported conflicting results on the effectiveness of high-dose chemotherapy with autologous stem cell support compared to conventional chemotherapy as part of first-line treatment in patients with aggressive Non-Hodgkin Lymphoma (NHL). We here report our updated meta-analysis to better define the role of HDT in these patients.

Methods: RCTs were identified by computerized search and handsearching of medical databases (Medline, Embase, Cochrane Library) and conference proceedings. Data extraction from published reports and quality assessment were done independently by two reviewers. In addition first authors supplied us with individual patient data. The hazard ratio (HR) was used as a measure of treatment effect; the inverse variance method (fixed effect model) was used for pooling. The relative risk was determined for binary data and pooled with the Mantel-Haenszel method (fixed effect model).

Results: 15 RCTs including 3,079 patients were eligible for this meta-analysis. 14 studies included 2,622 patients were evaluated. Complete response rates were significantly higher in patients receiving HDT (RR 1.10, 95% CI 1.03 to 1.17, 13 trials, n=2,018). However, there was no evidence for improved event-free survival for HDT compared to conventional chemotherapy (HR 0.93, 95% CI 0.81 to 1.07, 11 studies, n=1,601). There was also no evidence for an overall survival benefit for HDT compared to conventional chemotherapy (HR 1.00, 95% CI 0.84 to 1.19, 13 trials, n=2336). IPI subgroup analysis: There was no evidence for an overall survival benefit for IPI high-intermediate and high-risk patients receiving HDT compared to conventional treatment (HR 0.97, 95% CI 0.83 to 1.13). In IPI low/low-intermediate risk patients there was a trend for worse survival for HDT compared to conventional chemotherapy (HR 1.41, 95% CI 0.95 to 2.10). The difference in OS between low/low-intermediate and intermediate-high/high risk IPI subgroups was not statistically significant. There was no association between additional variables analyzed (proportions of diffuse large cell lymphoma, protocol adherence, HDT- and conditioning regimen used, response status of patients before HDT, and methodological issues) and the results reported here.

Conclusion: Despite higher complete response there is no evidence that HDT in first-line treatment of patients with aggressive NHL improves overall survival or event free survival.

MYELOABLATIVE ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT (ALLOGRAFT) FOR NON-HODGKIN'S LYMPHOMA (NHL): 20-YEAR EXPERIENCE WITH FAMILY MEMBER AND UNRELATED UNRELATED DONORS (UD)

C. Tute1, M. Barnett1, J. Corson2, D. Forrest1, R. Gascoyne1, D. Hogge1, J. Lavoie1, S. Nantel1, T. Nevill1, J. Shepherd1, K. Song1, H. Sutherland1, N. Voss1, C. Smith1
1Leukemia/BMT Program of British Columbia, Vancouver General Hospital, Vancouver, Canada; 2Medical Oncology, BC Cancer Agency, Vancouver, Canada; 3Pathology, BC Cancer Agency, Vancouver, Canada; 4Radiation Oncology, BC Cancer Agency, Vancouver, Canada

Since 1985, 103 NHL patients (pts) received myeloablative allo HSCT at the Leukemia/BMT Program of BC and have been followed for a minimum of 2 yrs (median 6, maximum 13). Median age was 39 (range 15–55 yrs): M/F 58:45. Median interval from diagnosis (dx) – HSCT was 1 yr (range 1 month–11 yrs); NHL dx were indolent (38%), aggressive (including transformed (6), 50) and special (Burkitt’s or lymphoblastic, 15). Graft-versus-disease (GVHD) prophylaxis included cyclosporine+– methotrexate in most (90); T-cell depletion was used in 3. Donors were matched related (rd) (76), mismatched (mm) (rd) (3), and ud (24) (including 4 mmud); 95 received marrow, 8 peripheral blood. Conditioning was cyclophosphamide (CY)+ total body irradiation (TBI) (80), CY/TBI – other (17), and busulfan (BU) + other (6). Disease status was early (7), intermediate (59) and advanced (34). 45 pts are alive; 58 are deceased, with relapse (REL, 28), or non-relapse mortality (NRM, 30). NRM was due to GVHD (9), RRT (14), infection (3) and other (4). Most deaths (47) occurred at <1 yr, 6 at 1–4 yrs and 5 >4 yrs. Donor lymphocyte infusion (DLI) was used in 6 REL pts, 1 survives. 10 yr overall (OS) and event-free survival is 41%, with no significant difference between indolent (48%), aggressive (36%) and special (47%). Cumulative incidence of AGVHD gr ≥ II; CGVHD; NRM; and REL is 38%; 69%; 30%, and 30%. Relapse risk did not differ between indolent, aggressive, or special. OS was improved in pts receiving CY/TBI (RR = 0.4, P = 0.04), and pts developing chronic GVHD (RR = 0.7, P = 0.04); pts with NHL did poorly (RR = 2.7, P = 0.01). This long-term study of NHL allograft pts demonstrates impressive 10-yr OS at 40%. Furthermore, successful results have been achieved in all three major subtypes of NHL.

TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS-RELATED LYMPHOMA WITH RISK-ADAPTED INTENSIVE CHEMOTHERAPY: FINAL ANALYSIS OF THE NHL-HIV 93 TRIAL BY THE GELA-GIACIT INTERGROUP

Hematology, GELA, France

Background: Treatment of AIDS-related lymphoma (ARL) is still controversial, as intensive chemotherapy could exacerbate immunodeficiency, with subsequent adverse effects for patients. We aimed to compare the effectiveness of risk-adapted intensive chemotherapy in patients with ARL treated in the NHL-HIV 93 randomized trial, before and after the use of highly active antiretroviral therapy (HAART).

Methods: 485 patients aged from 18 to 67 years were randomly assigned to CHOP based chemotherapy with a pretreatment stratification according to the HIV score which is based on performance status, prior AIDS and CD4+ cell counts <0.1 G/l. Chemotherapy was administered in conjunction with HAART for the 187 patients enrolled after June 1996. Three main histologic types of NHL were represented in the study population: diffuse large cell lymphoma (54%), Burkitt lymphoma (20%) and immunoblastic lymphoma (17%).

Results: With 6 years median follow-up, in the low risk group (HIV score = 0, n=218) the OS was estimated at 51% for high-dose CHOP
HIGH-DOSE THERAPY (HDT) AND AUTOLOGOUS STEM CELL TRANSPLANT (ASCT) AS 1-LINE TREATMENT IN PERIPHERAL T-CELL LYMPHOMAS (PTCL)


1Hematology, Aarhus University Hospital, Aarhus C, Denmark; 2Oncology, Radiumhospital, Oslo, Norway; 3Pathology, Radiumhospital, Oslo, Norway; 4Oncology/Hematology, Oulu Hospital, Oulu, Finland

Introduction: PTCL have a poor prognosis. ASCT has a favourable impact in relapsed PTCL. We here present the results of the largest PTCL trial published so far, based on a dose-intensified schedule including ASCT as 1-line strategy in PTCL.

Methods: The study is an ongoing multicenter phase II trial recruiting newly diagnosed PTCL aged 18-67 yrs. It evaluates response, toxicity, time-to-treatment failure (TTF) and overall survival (OS) after 6 courses of two-weekly CHOP (CHOP for age 61-67 yrs) followed by HDT with ASCT in first PR/CR.

Results: The present analysis is based on 64 confirmed PTCL cases. They had a M/F ratio of 1.9 and a median age of 54 yrs (range 24–66 yrs). Histological subtypes included PTCL unspecified n=30, alk-negative anaplastic large cell n=13, angioimmuno-blastic n=9, enteropathy type n=5, panniculitis type n=3, nasal type n=2, and hematopoetic n=2. At diagnosis, most patients had primary nodal disease. Although B-symptoms and elevated s-LDH were rather common, the majority of the patients presented with a good performance score (WHO 0–1). So far, induction outcome has been reported in 47 of the 64 patients. Of those, 43 (91%) achieved either a complete (38%) or a partial (33%) response after the first 3 induction courses. CRs moved to 50% and PRs to 35% after the 6th course. Treatment-related toxicity was manageable. Of the 47 patients, 33 (70%) moved on to transplant. Of these, 27 (82%) achieved a CR/CRu and 5 (15%) a PR post-transplant. In 13 patients post-transplant follow-up data were available: 11 (85%) of them are in continuous CR one year after transplant.

Conclusions: The present data show that a time-and dose-intensified induction schedule followed by 1-line HDT with ASCT is feasible and effective in previously untreated PTCL. Long-term remissions achieved by most of the patients. Longer follow-up is necessary to confirm long-term remission rates and evaluate their impact on TTF and OS.

OUTCOME OF PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA IN A SINGLE INSTITUTION: THE BRITISH COLUMBIA EXPERIENCE

K. J. Savage1, N. Al-Rajhi1, N. Voss, R. Klasa, R. D. Gascoyne, I. M. Connors2

1British Columbia Cancer Agency, University of British Columbia, Vancouver, BC, Canada

Introduction: Primary mediastinal large B-cell lymphoma (PMBCL) is a distinct clinicopathological subtype of diffuse large B-cell lymphoma. The optimal treatment is unknown with some studies suggesting a superior outcome with dose-intensive chemotherapy regimens and the role of radiotherapy remains ill-defined. We sought to characterize all patients with newly diagnosed PMBCL treated in a uniform manner by the lymphoma tumor group (LYTG) guidelines of the British Columbia Cancer Agency (BCCA).

Methods: The BCCA lymphoma database was searched and records reviewed to identify those patients presenting with a prominent mediastinal mass and considered to be PMBCL based on the current REAL/WHO classifications. Patients were generally treated based on era-specific BCCA guidelines (1980–1992: VACOPB; 1992–2001: CHOP-type; 2001—present CHOP/R). Beginning in January 1998 IFXRT was recommended by the LYTG to be routinely administered following chemotherapy. Prior to this, use of radiotherapy was individualized in advanced disease.

Results: In total, 153 patients with newly diagnosed PMBCL were identified between July 28, 1980 and June 30, 2003. The median age was 37 yrs (13–82), with 44% females. The majority had stage III (74%), bulky mediastinal disease (75%) with intra-thoracic extension (76%) and progression-free survival (PFS) at five years for the entire cohort were 75% and 69%, respectively. The international prognostic index (IPI) was predictive of survival (5-yr OS IPI 0.83%; IPI 2.5 71%; IPI 4.5 52%; P=0.003), although few patients fall into the high risk (IPI 4.5) group (11%). Five-year OS in patients <65 treated with VACOPB/MA-COPP was 87% (n=46) compared with 71% (n=63) in patients treated with CHOP-based chemotherapy (excluding CHOPR) (P=0.02). In comparison to CHOP, the 5-yr OS of patients receiving CHOPR (n=11) was 89% (P=0.48). Eleven patients received brief chemotherapy (CHOP-type×3 cycles) followed by IFXRT for presumed limited stage disease (5-yr PFS 82%). In an intention-to-treat analysis comparing the era before January 1998 (pre-IFXRT era) and the post-IFXRT era, there was no difference in 5 yr PFS (74% vs 92%; P=0.09) or OS (78% vs 69%, P=0.14).

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Conclusions: In this single institution, population-based retrospective study, we found that PMBCL patients have an excellent survival rate that appears to be superior to DLBCL. The IPI maintains its predictive utility in this disease, however, even the highest-risk group demonstrates a moderate survival advantage compared to DLBCL. Analysis of specific treatment regimens suggests that dose-intensified MACOPB or VACOPB results in improved outcome compared with standard CHOP-like regimens, in keeping with some prior reports. The addition of radiotherapy does not appear to improve survival. With the availability of FDG-PET, high risk patients that may benefit from radiotherapy may be better identified.

CHLORAMBUCIL VERSUS OBSERVATION AFTER ANTI-HELICOBACTER THERAPY IN LOW-GRADE GASTRIC LYMPHOMA: RESULTS OF THE INTERNATIONAL LY03 TRIAL

B. Hancock, D. Linch, J. Delchier, W. Qian, P. Smith, A. Wotferspoon, C. Copie-Bergmann, C. Truelle, S. Cortellazzo, F. Ferroni, A. Ambrosetti, G. Pinotti, F. Cavalli, R. Souhami, E. Zucca

1Lymphoma Clinical Studies Group, UK National Cancer Research Institute, UK; 2Groupe d’Etude des Lymphomes de l’Adulte (GELA), France; 3International Extranodal Lymphoma Study Group (IELSG), Switzerland

Introduction: Low-grade gastric lymphoma (LGG-L) is an uncommon tumour characterised by an indolent natural history and a tendency to remain localised for long periods. Chemotherapy is increasingly employed in the primary treatment of high-grade gastric lymphoma but its value in low-grade disease is unclear. No randomised trials of treatment in LGG-L have been undertaken. The aetiological relationship between gastric mucosa associated lymphoid tumours (MALT) lymphoma and H. pylori is intriguing. The LY03 was designed to establish whether treatment for H. pylori, or the subsequent addition of chlorambucil would cure gastric MALT lymphoma and prevent its recurrence.

Methods: Patients with non-resected, partially or completely resected LGG-L, stage I were registered in LY03 and treated with antibiotics for H. pylori infection. Those with successful eradication of H. pylori and no evidence of progression of the lymphoma were randomised to chlorambucil or observation. The primary outcome was recurrence rate.

Results: 233 patients were registered internationally with median age of 64, male 49%. H. pylori infected 86%, ECOG PS 0–1 98%, and no resection 93%. 97% patients had H. pylori eradicated after antibiotics, of those with abnormal mucosa at registration, 63% achieved macroscopically normal gastric mucosa. 102 patients were randomised (52 chlorambucil, 50 observation). Baseline characteristics were well matched. With a median follow-up of 52 months, 5 patients were dead and 21 progressed. The recurrence rates at 3 years from randomisation were 21% for chlorambucil, and 37% for observation, P = 0.15. 5-year recurrence-free and overall survival (95% CI) were 67% (56%, 78%) and 91% (83%, 98%), respectively.

Conclusions: There is no good evidence that chemotherapy contributes to prevention of recurrence in LGG-L base on these early results.
NATIONALWIDE INTEROBSERVER VARIATION IN THE DIAGNOSIS OF FOLLICULAR LYMPHOMA: A REPORT FROM THE PATHOLOGISTS OF GISL (GRUPPO ITALIANO STUDI LINFOMI)

C. Tripodi1, M. Paulli2, M. Sirotti2, G. Lo Bosco2, M. Federico2, V. Franco2
1Istituto di Anatomia ed Istologia Patologica, Università degli Studi di Palermo, Palermo, Italy; 2Istituto di Patologia Umana ed Ereditaria, Università di Pavia, Pavia, Italy; 3Gruppo Italiano Studio Linfomi, Università di Modena, Modena, Italy; 4Dipartimento di Matematica e Applicazioni, Università degli Studi di Palermo, Palermo, Italy

Introduction: Interobserver variability may occur in FL diagnosis, even when the diagnosis is performed by expert haematopathologists. Very limited informations are currently available on the reliability of FL diagnosis performed in laboratories on a national scale, where the lymphoma diagnosis is not always carried on by expert haematopathologists. In this study, the reproducibility of the FL diagnosis and related grading system was tested by a group of pathologist members of the Gruppo Italiano Studio Linfomi (GISL).

Methods: A board of 36 Italian pathologists, including expert haematopathologists as well as general pathologists, independently evaluated 92 cases of FL randomly selected from a retrospective GISL FL clinical trial. A data collection form was provided for each pathologist in order to gather the following information on the diagnosis, grading and pattern (nodular vs diffuse) of the cases reviewed. The data were statistically analysed (kappa statistics) to evaluate the concordance expressed by the board of pathologists.

Results: A prevalent diagnosis of FL was made in 68 cases (74%). In 17 cases (18%), the prevalent diagnosis was that of a histotype other than FL. Among these cases, the diagnosis of diffuse large B-cell lymphoma was the most frequent (7 cases), while in 6 cases no histotype was found to be prevalent. Of the remaining 7 cases, 5 were considered not evaluable and 2 had a prevalent diagnosis of non lymphoma. The kappa index showed a good agreement (K=0.65) on the differential diagnosis between lymphoma and non-lymphoma. The reliability of FL diagnosis as the differentiation of FL from other histotypes proved to be fair (K=0.34). A poor agreement was obtained when considering the grading (K=0.18) and pattern (K=0.15).

Discussion: Among a representative group of Italian pathologists with different levels of experience, the reproducibility of the diagnosis of FL seems to be quite satisfying, but the assessment of grading is still far from achieving a consensus. This latter finding is in keeping with previous experiences, which indicate that the present FL grading system has limited value because of its poor reproducibility. Variability of the slide quality due to incomplete standardization in tissue handling and staining and the difficulty of clear-cut distinction between centroblasts and blast-like cells with variant morphology may represent main misleading factors.

INTRA-FOLLICULAR PROLIFERATION RATE IS SUPERIOR TO HISTOLOGICAL GRADING IN PREDICTING OUTCOME IN FOLLICULAR LYMPHOMA

A. Kostel1, H. Tromp2, J. Raemaekers1, M. MacKenzie1, G. Born2, J. van Krieken1
1Hematology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands; 2Pathology, Radboud University Medical Centre Nijmegen; 3epidemiology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands

To predict outcome in follicular lymphoma (FL) histological grading is widely used, but it is poorly reproducible. Scoring systems such as the (FLIPI) consist of surrogate clinical markers that may reflect underlying biological phenomena. We investigated the prognostic value of the proliferation rate of the intra-follicular neoplastic cells in FL. Proliferating cells were identified by using the Mib-1 antibody in pre-treatment lymph node biopsies of 51 patients. In each section 200 cells per follicle were assessed in five follicles. The proliferation index (PI) was defined as (no. of Mib-1 positive cells/ total no. of cells) x 100. The inter-observer variability was assessed by repeating this procedure for 25 cases by a second investigator, resulting in a correlation coefficient of 0.81 (P<0.001) and a coefficient of variation of 1.14. All patients participated in a prospective trial on first-line treatment with the combination of CVP (cyclophosphamide, vincristine and prednisone) chemotherapy plus interferon-alpha2b, followed by interferon-alpha maintenance in responding patients. The median age of the patients was 53.3 years; 37 patients had a previous IV disease; in nine patients a wait and see interval preceded the treatment (median duration 13 months). A low IPI score was present in 27 patients, intermediate in 20 and high in one. (three patients unknown). At revision, six patients were classified as grade 3 FL, 45 as grade 1 or 2. The overall median PI was 16.9 (3.1-49.2).In grade 1 and 2 FL the median PI was 16.1, in grade 3 it was 24.2 (P = 0.02). After a median follow-up of 71 months the median progression-free survival (PFS) for all patients was 25 months. The median PFS was not reached in the patients with PI below the median compared to only 15 months in the patients with the PI above the median (P = 0.0005). In patients with the PI below median, overall survival was not reached compared to only 42 months in patients with a high PI (P = 0.0019). When the six patients with grade 3 FL were excluded from the analysis, the results remained significant. Male sex, bulky disease and intermediate or high IPI were also associated with adverse prognosis, whereas histological grade did not predict outcome. In multivariate analysis the impact of PI on OS remained significant. In FL intra-follicular proliferation rate is a strong independent prognostic factor of PFS and OS and superior to grading. PI assessment is simple and reproducible. The intra-follicular PI could be used instead of histologic grading in identifying the aggressive types of follicular lymphoma, requiring other types of treatment.

BURKITT-LIKE FEATURES IS ASSOCIATED WITH A POOR PROGNOSIS AND C-MYC AMPLIFICATION IN NHL

D. Damotte1, H. Mossaafa2, A. Jenabian2, R. Delarue1, A. Vincenness2, I. Aumouroy1, R. Jeandel1, E. Khoury1, J. Martelli1, T. Samson2, S. Tupia1, G. Flandrin3, X. Troussard1
1Pathology department, HEGP, Paris, France; 2Cytopathic, Laboratoire Pasteur-Cerba, Cergy Pontoise, France; 3Onco-Hematology, HEGP, Paris, France; 4Hematology, Neckcr, Paris, France

Introduction: In this retrospective study, we identified a subgroup of poor prognosis lymphomas with the presence of Burkitt Like Cells (BLCs)and carrying the c-MYC gene amplification without translocation (t(8,14), t(8,15), t(8,16). These histological/cytological and cytogenetical prognosis markers are independent from the lymphoma subtype as we report six follicular lymphomas, four mantle cell lymphomas, two marginal zone lymphomas, two diffuse large B cell lymphomas and one T cell lymphoma.

Material And Methods: Diagnosis were established by morphology, immunophenotyping, conventional cytogenetic, and FISH studies with commercially available probes.

Results: Morphological examination and/or histology showed BLCs in all patients, but without the Burkitt typical phenotype CD20+, CD10+ and BCL2+. Mean of Ki-67 positive cells percentage was 89% (range 70–100%). Karyotype was normal in 3 cases and complex in 12 cases (80%). Combined conventional cytogenetic and FISH studies, never detected the t(8,14), or its variants t(2;8) and t(8;22). C-Myc amplification was observed in all cases with 3 to more than 9 copies in 10–77% metaphase or interphase cells. Follicular lymphoma (FL) diagnosis was made with immunophenotype, typical t(14;18) and IgH/Bcl-2 fusion gene. Mantle cell lymphoma (MCL) of blastic variant was made with immunophenotype, typical t(11;14) or complex caryotype including 11 and 14 chromosome abnormalities and IgH/Bcl-1 fusion gene. Two MZL CD5– and CD10– had a complex caryotype including t(3) and t(18).

Conclusion: BLCs histological and cytological detection could be a new interesting marker of lymphoma poor outcome with c-Myc amplification as eight out of the 15 patients died after the diagnosis (53%), 7 within the first 6 months. This marker is predominant in older patients and is independent from lymphoma subtype.

MEMBRANE EXPRESSION OF PKC-BETA 2 PROTEIN IDENTIFIES A SUBGROUP OF PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA WITH POOR SURVIVAL

J. Briones, I. Espinoza, R. Bordes, A. Ferrer, S. Brunet, R. Martin, A. Sureda, J. Pratt, J. Sierra
Departments of Clinical Hematology and Pathology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
STUDY OF THE TREATMENT AND BIOLOGY OF LYMHO-MATOID GRANULOMATOSIS (LYG); A RARE EBV LYMPHOPRO-LIFERATIVE DISORDER

1Center for Cancer Research, National Cancer Institute, Bethesda, USA;  
2Laboratory of Cellular Immunology, National Institute of Allergy and Infectious Disease, Bethesda, MD, USA

LYG is a rare angiocentric-destructive process with EBV+ B-cells and reactive T-cells. LYG is graded with grades I-II showing rare-moderate large EBV+ B-cells (usually polyclonal or oligoclonal) and grade III showing numerous large EBV+ B-cells (usually monoclonal), likely reflecting progressive transformation. Historically, steroids and/or chemotheraphy have a 14 mos median survival. We are investigating Interferon-α (Ia-α) for grade III and dose-adjusted EPOCH +/- Rituximab for grade III LYG. Characteristics of 40 pts are: male sex 65%; median age (range) 56 (18-82); median ECOG PS 1 (0-3). Disease sites include lung 98%, CNS 30%, kidney 23%, skin 23%, liver 20% and nodes 8%. LYG grades are I-25%, II-25% and III-52%. Prior treatment was none 25%, chemotherapy +/- R-35%, and steroids alone-30% of pts. For grades III, Ia-α is begun at 7.5 million IU TIW and escalated as tolerated until disease regression and continued 1 yr after CR. Among 27 pts (2 NE), 56% are in continuous CR for a median of 52 mos (3-153). In 12 pts who progressed on Ia-, grade III was found in 9. Thus, in 19 pts with only grade II, 84% achieved sustained CR with Ia-α. In 11 evaluable pts with CNS disease, 64% achieved remission with Ia-α alone. The median time to remission is 10 mos (2-40) and median Ia-α dose is 20 MIU (7-40). 19 pts received DA-EPOCH +/- R. Of 15 pts (4 TE), 40% achieved CR. At a median FU of 46 mos, OS and PFS are 69% and 82%, respectively. One pt on Ia-α died from sepsis. Median EBV viral loads in 29 pts at study entry were 18 copies/10⁶ genome equivalents (0-22727) (normal=200). Lymphocyte subsets in 30 pts showed a median CD4:CD8 cells/mm³ (24-2322) and CD8:CD165 cells/mm³ (42-1316). In 12 pts in CR and with serial values, the mean CD8 cells (131 ± 44) (P=0.013) but not CD4 cells (65 ± 75) increased with treatment. High dose Ia-α produces sustained remissions in grade III LYG, and is effective in CNS LYG. DA-EPOCH +/- R can produce durable CRs in grade III LYG. These results suggest that EBV immortalized B-cells in grade III LYG retain sensitivity to immuno-surveillance. We hypothesize LYG emerges in a partially compromised immune milieu and undergoes progressive transformation if not effectively treated. Historical results and our data suggest that steroids may enhance transformation by compromising immune function. Accrual continues.

HETEROGENEITY OF EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE: NATIONAL SURVEY OF KOREAN CANCER STUDY GROUP

S. Lee, W. Kim, Y. Park, Y. Kang, S. Kim, Y. Hong, D. Kim, C. Kim, D. Hoo.  
Lymphoma Subcommittee, Korean Cancer Study Group, Seoul, Republic of Korea

INTRODUCTION: The WHO criteria of extranodal NK/T cell lymphoma, nasal type (NTCL) describes a homogeneous entity, but clinical heterogeneity does exist.

METHODS: Cases of NTCL based on histologic (angiocentricity, necrosis, and pleomorphic infiltration) as well as immunohistochemical criteria (CD3e+ and/or CD45RO+) were evaluated for clinical correlation and EBV in situ hybridization test. Results: 249 newly diagnosed Korean patients were included for analysis. Complete response rates to the initial chemotherapy and/or radiation and overall survival were distinctively different among groups categorized according to the major sites of involvement and the Ann Arbor staging.

Long-term survivors were observed mainly in stage III patients with nasal presentation and poor prognosis was associated with extranodal involvement. IPI score predicted survival as well.

Conclusion: A subset of extranodal presentation without nasal lesion is unique in low frequency of EBV positivity and poor prognosis in NTCL.
BLASTIC NK CELL LYMPHOMA OF THE WHO CLASSIFICATION: A NOVEL DISEASE DERIVED FROM PLASMACYTOID DENDRITIC CELLS

H. Ebbhardt, H. Stein
Charité–Universitätsmedizin Berlin, Campus Benjamin Franklin, Institute of Pathology, Berlin, Germany

Introduction: In the WHO classification CD4+ CD56+ neoplasms are termed blastic NK-cell lymphomas. Recent data, however, challenges their cellular origin. Here we provide and confirm evidence that most of the so-called blastic NK-cell lymphomas are not related to NK cells but to the recently recognized plasmacytoid dendritic cells (pDC).

Methods: CD4+ CD56+ NK-cell like tumours were selected from the archives of the Berlin Reference Centre for Haematopathology and from the EAHP Slide Workshop 2004. Molecular features of the tumour cells were compared with those of other malignancies and reactive lymphatic lesions. Clinical data were compared with those reported in the literature.

Results: Among the CD4+ CD56+ tumours examined most expressed TCL1, CD123, CD43, HLA-DR and CD45RA. The tumours variably expressed CD68 and TdT; they were consistently negative for myeloperoxidase, CD3 and CD45RO. These neoplasms are associated with characteristic clinical features.

Conclusion: The neoplastic cells of most so-called blastic NK-cell lymphomas resemble more closely the recently recognized pDC-population rather than NK cells. Thus these neoplasms represent a novel type of tumour which are probably derived from pDC, and are characterized by surprisingly homogeneous molecular and clinical features.

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GASTROINTESTINAL INVOLVEMENT IN MANTLE CELL LYMPHOMA (MCL). A CLINICOPATHOLOGIC STUDY

A. Salar1, N. Juanpere2, B. Espinet2, E. Domingo2, A. Seoane2, B. Bellvisillo2, A. Panades4, V. Romagosa2, E. Abella2, C. Pedro2, F. Solé2, E. González-Barca2, C. Besset2, S. Serrano2
1Clinical Hematology, Hospital del Mar, Barcelona, Spain; 2Pathology, Hospital del Mar, Spain; 3Hematology, ICO-Bellvitge, Spain; 4Endoscopy, Hospital del Mar, Spain

Objective: to investigate the clinical, endoscopic and microscopic involvement of the GI tract in a prospective series of MCL.

Methods: 11 patients with MCL have been consecutively entered in a staging workup that includes upper and lower endoscopy of the GI tract. Multiple biopsies of the stomach and colon were taken from abnormal mucosa and from macroscopically normal mucosal. Specimens were assessed immunohistochemically, with FISH and PCR.

Results: Only 1 patient presented with GI symptoms at diagnosis. Endoscopy: Upper GI: 36% showed mild erythema and in the remaining patients it was absolutely normal. Lower GI: 9% showed mild erythema, 27% had polyps and in the remaining patients it was normal. In global, 64% of patients had abnormal endoscopies. Pathology: Upper GI: 89% of patients had microscopic infiltration and MCL was confirmed in 78%. Lower GI: 89% of patients had microscopic infiltration and MCL was confirmed in 67%. Microscopic features and immunohistochemistry according to endoscopic findings:

<table>
<thead>
<tr>
<th>Endoscopy</th>
<th>Lymphoid infiltrates or nodules (%)</th>
<th>CD20+CD5 + (%)</th>
<th>Cyclin D1 + (%)</th>
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<tr>
<td>Upper GI</td>
<td>Abnormal</td>
<td>100</td>
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<td></td>
<td>Normal</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>Lower GI</td>
<td>Abnormal</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>83</td>
<td>50</td>
</tr>
</tbody>
</table>

All positive cases for CD20 and CD5 were positive for cyclin D1. FISH analysis with the BCL1/IgH probe (Vysis) and PCR studies are under evaluation. In global, all patients had MCL involvement of the GI tract, determined by combination of microscopic examination and immunohistochemistry. Even a patient with MCL isolated in tonsils had microscopic involvement of the stomach.

Conclusions: In our series, GI involvement by MCL was detected in all patients. All patients with endoscopic abnormalities had microscopic MCL and in more than half of the patients with normal mucosa, GI tract involvement could be demonstrated at the microscopic level. Immunohistochemistry with CD20, CD5 and cyclin D1 was more useful than FISH.

ATYPICAL CYTOGENETIC PRESENTATION OF T(11;14) OCCURRED IN MORE THAN 17% OF MANTLE CELL LYMPHOMA PATIENTS

S. Gazzo, P. Felmans, F. Berger, B. Coffier, J. Magaud, E. Callet-Bauchu
Services d’Hématologie et d’Anatomie Pathologique, Centre Hospitalier Lyon Sud – Hospices Civils de Lyon, Pierre-Bénite Cedex, France

Introduction: If karyotypic analysis (KA) of mantle cell lymphoma (MCL) demonstrated the presence of the t(11;14) translocation in 75% of cases, the abnormality is identified in virtually all cases when FISH studies using specific probes are performed. Up to now, rare cases of complex t(11;14) have been described on KA. Based on the analysis of 103 MCL patients with clonal karyotypic changes, we report 18 cases in which the t(11;14) presented an atypical pattern, that could lead to a misclassification.

Methods: The LSI IgH/CND1 dual color probe was used for FISH investigations. As a result of the translocation 2 fused orange-green signals are identified, in addition to 1 orange and 1 green signals corresponding to the normal chromosomes 11 and 14, respectively (2F/1O/G).

Results: According to the KA and FISH studies, 3 atypical presentations were observed: 1) presence of unidentifiable material on the long arm of the der(14) [9 pts]; 2) presence of additional material on the short arm of the der(14) [5 pts]; 3) insertion of the translocation within an extra chromosome [4 pts]. The typical 2F/1O/G pattern was observed in 13 patients whereas 3F/1O/G, 4F/1G/O and 5F/2O/2G, corresponding to duplications of the translocation were identified in 3, 1 and 1 patients, respectively.

Conclusions: This data demonstrates that atypical t(11;14) presentations are not so infrequent events in MCL, occurring in about 1/6 (17%) patients. In addition, unsuspected sub-microscopic or duplicated cases can occur in at least 5% of patients. This therefore underlines that FISH using specific probes is highly recommended, particularly in cases with an atypical presentation on KA. In addition, further studies are required to ascertain if atypical presentations, and particularly duplicated cases, experienced a more aggressive clinical course, as exemplify in chronic myeloid leukemias displaying duplications of the Philadelphia chromosome.
17. Paediatric Lymphomas

THE 15–20 YEAR OLD PATIENTS WITH NHL TREATED IN FRANCE: DATA OF CHILDHOOD AND ADULT DATABASES
C. Patte1, A. Auperin2, C. Sebban1, C. Bergeron1, C. Gisselbrecht2, V. Ribrag1, F. Reyes1, L. Brugieres1
1Societe Francaise d’Oncologie Pediatrique, (SFOP), France; 2Biostatistics, IGR, Villejuif, France; 3Groupe d’Etudes des Lymphomes de l’Adulte, (GELA), France

Introduction: There are very few data on adolescents (ados) [15–20 years (y)] with NHL and little is known about their clinical presentation, type of NHL, phase of treatment (Tx), type and outcome of Tx.

Methods: We merged the data of the 15–20y old patients (pts), extracted from the childhood (C) SFOP LMB89-84, LMB95-89, LMB96-92, LMB91-92, ALCL 99 databases and from the adult (A) GELA LMB87-93-98 and LMB95 databases covering time periods between 1984 and 2001.

Results: There were 341 eligible pts, 37% from the C database (age: 15–17.8, mean 15.5y) and 63% from the A (15–20, mean:18.6y). According to histology, 61% were mature B-cell (22% Burkitt (BL), 37% large B-cell (DLBL), 3% not determined), 17% lymphoblastic (Lb), 18% anaplastic large cell (ALC), and 4% other T peripheral. 68% pts had advanced stages (III or IV in the Ann Arbor or St Jude’s classification). LDH was \( > \text{N/2} \) in 43% and 26.5% pts respectively in the C and A databases. 3-y EFS were respectively in C and A: 80% and 68% for BL (ns), 77% and 83% (ns) for DLBL, 78% and 38% (P=0.004) for LB and 77% and 74% (ns) for ALC. Among B-cell NHL, EFS was 86% vs 71% when LDH was \( \leq \text{N/2} \) (P=0.006).

Conclusions: These preliminary data need to be refined and involved only pts included in therapeutic trials. It seems that once included in a study ados with NHL might have a similar probability of cure with the C and A regimens for B-cell NHL and ALC, but inferior for LB. Further analysis will be presented to address other questions, such as weight of Tx in the different regimens, and differences with the <15 and the >20y in term of biological, TX tolerance and outcome. These data represent a rational for other studies to optimize Tx for ados.

THE IMPACT OF AGE AND SEX ON INCIDENCE, BIOLOGY AND TREATMENT OUTCOME OF NON-HODGKIN LYMPHOMA IN CHILDHOOD AND ADOLESCENCE
B. Burkhardt1, M. Zimmermann1, I. Oschlies2, F. Niggli3, G. Mann1, M. Schrappe1, R. Pawarzech1, A. Reiter1
1Paediatric Oncology, University Hospital Giessen, Giessen, Germany; 2Lymph Node Registry, University Hospital Kiel, Kiel, Germany

Introduction: We analysed the impact of age and sex on biology and treatment outcome of NHL of childhood and adolescents

Patients and Methods: 2147 patients from Austria, Germany and Switzerland registered between 10/86 and 12/02 and treated according to multicentre cooperation study protocols NHL-BFM 86, 90, 95 were included in the analysis. Patients were classified according to the Kiel and the WHO-classification.

Results: The median age at diagnosis was 9.3 (0.2–18.5) years and was 8.0y for 97 pB-lymphoblastic lymphoma (pB-LBL)-patients, 8.8y for 335 T-LBL patients, 8.4y for 1004 Burkitt lymphoma/leukemia (BL/BL-A)-patients, 11.4y for 173 diffuse large B-cell lymphoma (centroblastic subtype) (DLBCL-CB)-patients, 13.2y for 40 primary mediastinal large B-cell lymphoma (PMLBL)-patients and 11.7y for 274 anaplastic large cell lymphoma (ALCL)-patients (P<0.000001). The male:female-ratio was 2.7:1 in the total group and was 0.9:1 for pB-LBL and PMLBL. 1.7:1 for DLBCL-CB, 2.5:1 for T-LBL and 4.6:1 for BL/BL-A (P<0.00001), pEFS(5y) was 84 ± 1% for all 2147 patients (median follow-up 3.5 (0.1–15.9) years). In the total group pEFS(5y) was 85 ± 1% overall, 84 ± 1% for females (P=0.05). For further analysis patients were classified into four age-groups: 0–4, 5–9, 10–14 and 15–18 years. pEFS was significantly superior for 5–9 year old patients compared to the youngest and the adolescent age-group. The inferior outcome of the 0–4y age group was due to the pB-LBL-patients (pEFS(5y) ± 12%, n=27) while the inferior outcome of the adolescent group was due to inferior pEFS of female T-LBL (pEFS(5y) ± 19%, n=10) and female DLBCL-CB patients (pEFS(5y) ± 21%, n=10).

Conclusions: The distribution of sex and age at diagnosis is significantly different between different NHL subtypes of childhood and adolescence. With the treatment applied, pEFS at 5 years was not significantly different according to sex and age except for 0–4y old pB-LBL patients and adolescent females with T-LBL and DLBCL-CB who had an inferior outcome.

DIFFUSE LARGE B-CELL LYMPHOMAS IN PEDIATRIC PATIENTS DEMONSTRATE A MARKED PREDOMINANCE OF GERMINAL CENTER CELL PHENOTYPE
Pediatrics, FAB/LMB 96 Study Group, Salt Lake City UT, USA

Introduction: Microarray studies of diffuse large B-cell lymphomas (DLBCL) in adults have identified gene expression patterns that correlate with prognosis including a germinal center (GC) pattern and an activated B-cell (ABC) pattern. Approximately 40–60% of adult DLBCL demonstrate GC expression patterns, which correlate with significantly better patient outcomes than ABC phenotypes. Immunohistochemistry (IHC) for CD10 and BCL6 are associated with a GC phenotype. DLBCL is less commonly seen in pediatric patients, but is associated with significantly better outcomes with approximately 85–90% cure rates in the recently completed FAB/LMB96 study. We hypothesized that the superior outcome seen in children with DLBCL may be associated with the phenotype.

In the present study, we did IHC (CD10, BCL6, MUM-1) on fixed tissue sections in 82 cases of uniformly treated pediatric DLBCL from the FAB/LMB96 study.

Results: 79/82 cases (96%) demonstrated a GC phenotype (positive for CD10, BCL6 or both). 23 of the cases that were not positive for CD10 or BCL6 stained for MUM-1, an ABC marker. All tumors demonstrated a relatively high proliferative index as measured by MIB-1 staining (mean of 73%, range 24–98).

Conclusions: The marked predominance of the GC phenotype in pediatric patients with DLBCL may contribute to the excellent prognosis relative to adults.

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMLBL) IN CHILDREN/ADOLESCENTS. DATA OF EUROPEAN AND AMERICAN GROUPS
C. Patte1, A. Reiter1, A. Rossolen2, M. Cairo1, B. Burkhardt1, M. Pillon2, F. Leyder1, A. Auperin2, M. Gerrard2
1Societe Francaise d’Oncologie Pediatrique, (SFOP), France; 2Biostatistics group, GPOH, Germany; 3Associazione Italiana di Ematologia e Oncologia Pediatrica, (AIEOP), Italy; 4Children Oncology Group, (COG); USA; 5Biostatistics, IGR, Villejuif, France; 6UK Children Cancer Study Group, (UKCCSG), UK

Introduction: PMLBL is a rare subtype of non-Hodgkin’s lymphoma (NHL). Optimal treatment strategies for paediatric patients (pts) are still to be established.

Methods: We looked at the data of the pts with PMLBL from the French LMB89, the Italian French-American-British FAB LMB96, the German-Austrian-Swiss BFM 86-90-95 and the Italian AIEOP LNHL 92–97 databases, covering periods between 1984 and 2003. Treatment regimens were either the LMB or the B-FBM strategy for mature B-cell NHL. Radiotherapy was not part of the strategy, but was used for Italian pts who did not achieve complete remission or relapsed.

Results: We identified 116 pts, which represents <2% of pts, except in the FAB/LMB96 series (3.8%) where US pts were registered until 21 years (t). 56% were female. Age was from 1.4 to 19.7, median 15y. There were 40 events: 1 toxic death, 17 no complete remission with the protocol and 22 relapses. 25 pts died. One major difficulty was the interpretation of a residual mediastinal mass. Prognostic factors were: LDH level >500 in the BFM series, and the association of size >10cm and LDH>30x2 in the FAB LMB96 series.

Conclusions: PMLBL is rare in children, so national series are small and do not allow clear conclusions to be drawn. The data from the different databases will be extracted, merged and presented. The pooling of these data should enable a better description of these pts, and improve

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the analysis of events and prognostic factors, and will be the basis for a collaborative prospective study.

A NOVEL APPROACH FOR STAGING AND MINIMAL RESIDUAL DISEASE DETECTION IN T-CELL LYMPHOBLASTIC LYMPHOMA—A CHILDREN’S ONCOLOGY GROUP STUDY
D. Campana, E. Coustan-Smith, J. Sandlund, M. Abromowitch
1Hematology-Oncology, St. Jude Children’s Research Hospital, Memphis, TN, USA; 2Pediatrics Hematology/Oncology, University of Nebraska Medical Center, Omaha, NE, USA

Introduction: Reliable prognostic indicators for children with T-cell lymphoblastic lymphoma (T-LL) are lacking. We are applying a flow cytometric method that can detect 1 malignant T-cell among 10,000 or more normal cells to assess disease dissemination at diagnosis in patients with T-LL enrolled in the COG A9791 study Randomized Phase III Study for the Treatment of Newly Diagnosed Disseminated Lymphoblastic Lymphoma or Localized Lymphoblastic Lymphoma. Because in patients with T-cell acute lymphoblastic leukemia levels of minimal residual disease (MRD) in peripheral blood resemble those in bone marrow, we hypothesized that blood could also be used for staging T-LL.

Methods: Expression of CD3 and TdT, combined with the absence of B-cell and myeloid antigens (a phenotype found in virtually all cases of T-LL but absent in normal tissues except the thymus) was used to identify malignant T cells among bone marrow and peripheral blood mononuclear cells.

Results: Among 45 patients studied to date, 35 (78%) had lymphoma cells detectable by flow cytometry in the bone marrow at diagnosis. Median percent CD3+/TdT+ cells was 0.5% (range 0.01%-28%) of marrow mononuclear cells, with few exceptions, lymphoma cells were undetectable by morphology. In 17 patients, we studied paired left and right iliac crest bone marrow samples: in all cases, results were concordant (14 positive and 3 negative), and the difference in percentages of CD3+/TdT+ cells measured among positive sample pairs was <1 log. In 39 of the 45 patients, paired bone marrow/peripheral blood samples were available for study. In 30 patients, CD3+/TdT+ cells were detected in both bone marrow and peripheral blood; levels of disease in blood were closely related to those in marrow. In the remaining 9 patients, bone marrow samples did not contain (<0.01%) CD3+/TdT+ cells; however, CD3+/TdT+ cells could be detected in 4 of the paired blood samples (0.01%, 0.01%, 0.09, 0.05%).

Conclusions: The method applied in this study may provide new insights about disease dissemination in T-LL patients. We suggest that flow cytometric analysis of peripheral blood could be used to monitor early response to treatment and MRD.

SALVAGE STRATEGY FOR ANAPLASTIC LARGE CELL LYMPHOMA IN CHILDREN: PROGNOSTIC IMPACT OF TIME OF RELAPSE AND CD3 REACTIVITY
1Pediatric Oncology, University Children’s Hospital, Gießen, Germany; 2Pediatrics, University Hospital, Berlin, Germany; 3St. Anna, Kinderspital, Vienna, Austria; 4Pediatric Hematology, Univ. Hospital, Tübingen, Germany; 5Lymphode Registry, Hemopathology, Kiel, Germany; 6Pediatric Oncology, University Children’s Hospital, Gießen, Germany

Introduction: We examined the feasibility and efficacy of a salvage strategy of intensive induction chemotherapy followed by autologous or allogeneic bone stem cell transplantation (B SCT) for children and adolescents suffering from relapsed anaplastic large cell lymphoma (ALCL) after BFM front-line therapy.

Patients and Methods: From 4/1990 to 2/2003, 77 patients, median age at relapse 9.8 (range 0.4–22.2) years, were enrolled. 2 pts with a history of lymphomatoid papulomatosis were excluded from further analysis. The median time from the start of first therapy to failure was 7.1 (range 1–76) months. 17 pts suffered from progressive disease during frontline therapy. CD3 reactivity was positive in 24, negative in 42 pts and not available in 7 pts. 2 pts had B-cell ALCL. salvage therapy consisted of 2 or 3, 5-day chemotherapy courses based upon dexamethasone, vincristine, doxorubicin, intrathecal therapy followed by BSCF. Conditioning regimens: TBI (2 × 2 Gy days 7–15, 25–27), etoposide 40 mg/kg day 1, 4. Cy 60 mg/kg/days 3–2. Data were updated as of April 1, 2004.

Results: The probability of survival at 3 years is 36 ± 6%. 28 pts died of lymphoma, 6 pts of toxicity. 41 pts CR2. 21 pts received additional chemotherapy only or no salvage (1 CR, 2 TMR, ≥2 are alive in 18 deaths of disease [dd]). 39 pts received autologous B SCT (21 CR, 2 TMR, 16 relapses [10 dd, 6 CR2]). 15 pts received allogeneic B SCT (10 CR, 3 TMR, 2 dd). 17 pts relapsed during front-line therapy of whom only 3 (15 ± 6%) survived (2 after autologous B SCT) compared to 37 of 57 (67 ± 9%) pts who relapsed later (>P<0.001). 62% of the pts with CD3 neg ALCI survived compared to 46% with CD3 pos. The relapse-free survival rate after autologous B SCT was significantly different according to the CD3 status: CD3 neg. 16/23 (70%); CD3 pos. 11/11 (96%) (<P<0.001).

Conclusion: This strategy proved feasible and efficacious for pts who suffered a relapse after front-line therapy while outcome for pts with progressive disease during front-line treatment was poor. The efficacy of autologous B SCT as consolidation depends on the CD3 expression status of the tumor cells.

DELETION OF CRANIAL IRRADIATION AND ADDITION OF SYSTEMIC HIGH DOSE METHOTREXATE AND INTRATHecal CHEMOTHERAPY RESULTS IN 78% 4-YR. EFS IN CHILDREN AND ADOLESCENTS WITH CNS POSITIVE B-NHL: RESULTS OF INTERNATIONAL FAB/LMB 96 STUDY
M. Cairo, M. Gerrard, R. Spoto, A. Auperin, R. Pinkerton, J. Michon, C. Weston, S. Perkins, M. Raphael, K. McCarthy, C. Patte
Pediatrics, COG, SFOP, UKCCSG, Columbia University, New York, NY, USA

Introduction: Previous studies in children and adolescents with CNS + B-NHL have required cranial irradiation (LMB-89) and have resulted in a 65–79% EFS with systemic intensive high-dose MTX (5–8 gm/m²) (Patte et al., Blood 2001).

Methods: As part of the FAB/LMB-96 study, pts with CNS + B-NHL did not receive cranial irradiation but instead received an additional course of HDDMTX (8 gm/m²) in between CYVE or nCYVE courses and additional intrathecal chemotherapy (Cairo et al., Blood, 492A, 2003).

Results: There were 113 pts with CNS + B-NHL; 60% BM +, median age 8 (2–19) yrs, M: F 4:6.1, LDH (g e 2XL) 70%; BL 78%; BIL 5% and DLBCL 11%. CNS + pts receiving standard FAB/LMB Tx had a 4-yr EFS of 71 ± 5.4% vs. LMB-89 Tx (included cranial irradiation) of 79 ± 5.6% (P = 0.14). Pts with CNS + only vs. CNS + BM had a significantly enhanced 4-yr EFS 82 ± 3.7% vs. 61 ± 6.0% (P = less than 0.001).

Pts with a non response to COP (<20%) had significantly inferior outcome compared to COP incomplete response (20–99%) and CR (100%) (3-yr EFS 44 ± 17% vs. 71 ± 4.7% and 100%) (P = less than 0.004).
LDH (g e 2XL) vs. LDH (NL), 4-yr EFS (63 ± 6 vs. 84 ± 5) (P = < 0.05).

Histology had no effect on EFS.

Conclusions: These international results suggest that deletion of cranial irradiation and replacement with additional HDDMTX (8 gm/m²) + IT Tx with standard FAB/LMB Tx still results in at least 70% EFS.

CYTOGENETIC ANALYSIS OF 237 PEDIATRIC MATURE B-CELL NON HODGKIN LYMPHOMA (NHL) CASES (FAB/LMB96) EXHIBITS SEVERAL PATTERNS OF CHROMOSOMAL ALTERATIONS AND NEW PROGNOSTIC FACTORS
1Genetics, Société Française d’Oncologie Pédiatrique, Paris, France; 2Genetics, Children’s Oncology Group, Arcadia, USA; 3Genetics, UK Children’s Cancer Study Group, Leicester, UK; 4Statistics, Société Française d’Oncologie Pédiatrique, Paris, France; 5Pathology, Société Française d’Oncologie Pédiatrique, Paris, France; 6Pathology, Children’s Oncology Group, Arcadia, USA; 7Pathology, United Kingdom Children’s Cancer Study Group, Leicester, UK; 8Pediatrics, United Kingdom Children’s Cancer Study Group, Leicester, UK; 9Pediatrics, Children’s
Oncology Group, Arcadia, USA; 10Pediatry, Société Française d’Oncologie Pédiatrique, Paris, France

Introduction: Burkitt lymphoma (BL) is the main childhood B-cell NHL characterized by the 8q24 translocation (t(8q24)) leading to a c-myc deregulation. Additional chromosomal alterations have been described in BL as well as in diffuse large B-cell lymphoma (DLBCL), but their prognostic value is not clearly evaluated, especially in children.

Methods: Karyotypes from 237 children enrolled in the FAB/LMB96 study were centrally reviewed by each participating cooperative group and obtained an international morphological consensus diagnosis: BL 76.8%, BL-like (BLL) 7.6%, DLBCL 12.2%, unclassifiable 3.4%.

Results: The BL/BLL were usually diploid with a t(8q24) in 92% cases and associated with other chromosomal alterations in 69%, mainly +1q (usually duplication), der(13q), +7q. The DLBCL were more heterogeneous and more complex than BL/BLL. t(8q24) incidence (35%) was higher than in adult DLBCL and the pattern of chromosomal alterations varied according to the presence of t(8q24) (+1q, del(6q), +7q) or not [more hyperdiploid, der(11q) and +12q]. Multivariate analysis identified two different associations of independent cytogenetic factors with worse prognosis on both overall survival and event free survival. Model (A): complex karyotype (more than 3 chromosomal alterations) [RR = 3, P = 0.001] and t(8q24) [RR = 5, P = 0.044]; or model (B): der(13q) [RR = 3.8, P = 0.001], +7q [RR = 2.2, P = 0.03] and t(8q24) [RR = 5.5, P = 0.04]. (+1q had no significant effect).

Conclusion: This study emphasizes the impact of cytogenetics in both diagnostic characterization and prognostic stratification of childhood mature B-cell NHL.

PROGNOSTIC FACTORS IN CHILDHOOD/ADOLESCENT B-CELL LYMPHOMA: RESULTS OF THE INTERNATIONAL FAB/LMB96 STUDY

C. Patte1, M. Gerrard1, A. Auperin1, J. Michon1, R. Pinkerton2, R. Spoto3, C. Weston1, S. Perkins1, M. Raphael1, K. McCarthy1, M. Cairo1
1Société Française d’Oncoologie Pédiatrique, (SFOP), France; 2UK Children Cancer Study Group, (UKCCSG), UK; 3Children Oncology Group, (COG), USA

Introduction: As in the SFOP LMB89 study, patients (pts) included in the FAB LMB96 international study were stratified for treatment (Tx) in 3 risk groups (gr): A (resected stage (st) 1 and abdominal st2), B (not in group A or C), C (CNS+ and L3ALL), and received Tx of progressive intensity. The randomised analysis indicated that Tx could be decreased in grB, but not in grC.

Methods: Final statistical analysis was done in January 2005 and a multivariate analysis performed in grB, the intermediate risk (IR) group which is the largest and most heterogeneous.

Results: 1109 evaluable pts were registered between 05–1996 and 06–2001: 132 grA, 743 grB and 234 grC. There were 11% st1, 20% st2, 44% st3, 9% st4 and 16% L3 ALL. With a median FU of 4.5 y, the 3y overall and event free survival was 91% and 89%. The 3y EFS by gr is: 98% grA, 90% grB, 79% grC (P<0.0001) and by st: 99% st1, 98% st2, 87% st3, 83.5% st4 and 79% L3ALL (P<0.0001). The multivariate analysis for EFS in grB showed that: st (3+4 vs 1+2, P = 0.01), LDH (>Nx2 vs <Nx2, P<0.0001) and mediastinal primary (P = 0.003), were prognostic factors (pc fr), that response at D8 was at the limit of significance (P = 0.07) and that age >15 y and histology (BL+BLL vs DLCL) were not. After adjustment for country, grade III–IV toxicity of first induction course and the identified pc fr, the pts who started the second induction course >D21 had a significantly lower EFS (88%) than those who started < D21 (94%, P = 0.007).

Conclusions: Using the LMB regimen where intensity is adapted to st, resection and response to Tx, EFS is high in a multinational study. In the IR gr (grB), st, LDH level and mediastinal primary are pc fr. Early (first month) Tx intensity is of major importance.
INCIDENCE, PREDICTIVE FACTORS AND OUTCOME OF TRANSFORMED LYMPHOMA: A POPULATION-BASED STUDY FROM BRITISH COLUMBIA

A. Al-Toumi1, M. Chahabba2, K. Gill1, P. Hoiski3, R. Klaas1, C. Patie1, K. Savage1, L. Sehn1, T. Shenkier1, R. Gascoyne2, J. Connors1
1Medical Oncology, BC Cancer Agency, Vancouver, Canada; 2Pathology and Laboratory Medicine, BC Cancer Agency, Vancouver, Canada; 3Biostatistics, BC Cancer Agency, Vancouver, Canada

Introduction: Development of large cell lymphoma in patients (pts) with indolent lymphoma is known as transformation (TRAN). The reported frequency is between 20–70%.

Methods: The BC Cancer Agency lymphoma database was used to identify all pts diagnosed with follicular lymphoma (FL), lymphoplasmacytic lymphoma (LPL) or small lymphocytic lymphoma (SLL) between 1986 and 2001. Exclusion criteria: diagnosis outside BC; marginal zone or MALT histology; HIV+; age <15 or >60 y; incomplete staging or refusal of treatment. TRAN was defined by either histological proof (HIST) or clinical features (CLIN), including: rapid nodal or extranodal growth; sudden rise in LDH to > baseline; involvement of unusual extranodal sites; or hypercalcemia. The extent of TRAN (limited vs advanced) was noted. Treatment at the Initial diagnosis of indolent lymphoma and after TRAN was noted. To identify factors that may predict for TRAN, a multivariate analysis of clinical and laboratory features at initial diagnosis was performed.

Results: 535 pts identified. Median age 49 y (21–60); histology, FL 458(86%), SLL 38(7%), LPL 39(7%). 139 pts developed TRAN. 89(64%) based on HIST. The majority of TRAN(s) were advanced, 109(78%). The median follow-up is 90 months (1–225). The 5 y risk of TRAN was 20%, with a continuous annual risk of 3%. The post-TRAN 5 y overall survival (post-T 5 y OS) of all 139 pts was 23%. Outcome was better after limited than advanced TRAN (post-T 5 y OS: 60% vs 13%, P=0.0001). The method of diagnosis of TRAN (CLIN vs HIST) had no impact on outcome (5 y post-T OS: 19% vs 26%, P=0.17). There was a significant difference in the risk of TRAN based on the initial treatment of the indolent lymphoma (P=0.0033). Advanced clinical stage and high LDH at initial diagnosis were predictive of TRAN (P=0.005 and 0.02 respectively).

Conclusions: The annual risk of TRAN is 3% for at least 15 y. Pts with limited TRAN have a better outcome. A CLIN diagnosis is equivalent to HIST proof in predicting outcome. Advanced stage and high LDH at diagnosis of indolent lymphoma independently predict for future TRAN.