4. Extramedullary Lymphomas I

ABERRANT SOMATIC HYPERMUTATION IN PRIMARY MED-IASTINAL LARGE B-CELL LYMPHOMA

D. Rossi1, M. A. C. Girolami1, D. Capello1, E. Berra1, C. Deambrogi1, S. Franceschetti1, C. Vendramin1, C. Rus1, A. Conconi1, M. Pauli2, S. Pileri2, G. Gadano1

1Hematology Unit, Department of Medical Sciences, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy; 2Pathology, Policlinico San Matteo, Pavia, Italy. 3Hematopathology Unit, University of Bologna, Bologna, Italy

Introduction: Primary mediastinal large B-cell lymphoma (PMBCL) is a subtype of diffuse large B-cell lymphoma (DLBCL) arising in the mediastinum. Compared to DLBCL, PMBCL displays specific clinico-pathologic features suggesting that it may represent a distinct entity. Aberrant somatic hypermutation (SHM) of multiple proto-oncogenes represents a molecular feature distinctive of DLBCL.

Methods: We performed mutational analysis of PIM-1, PAX-5, RHOFITF and c-MYC in a panel of 19 PMBCL and 19 DLBCL for comparison.

Results: The prevalence of mutated cases was similar between DLBCL and PMBCL. Mutations targeting at least one of the four genes were found in 14/19 (73.6%) PMBCL and 13/19 (68.4%) DLBCL; mutations in more than one gene were found in 7/19 (36.8%) PMBCL and 9/19 (47.4%) DLBCL. Among the four genes, the prevalence of mutated cases was also superposable between PMBCL and DLBCL: PAX-5 was mutated in 9/19 (47.3%) PMBCL and in 7/19 (36.8%) DLBCL; RHOFITF was mutated in 6/19 (31.5%) PMBCL and in 8/19 (42.1%) DLBCL; PIM-1 was mutated in 3/19 (15.7%) PMBCL and in 7/19 (36.8%) DLBCL; c-MYC was mutated in 6/19 (31.5%) PMBCL and in 5/19 (26.3%) DLBCL. The mutation pattern was also similar between PMBCL and DLBCL and was consistent with the pathological SHM process. Among PMBCL, the majority of the mutations were represented by single base-pair substitution (n=66), whereas only 8 deletions were observed. The transition/transversion ratio was 41/25 (1.64; expected 0.5; P<0.001). Eleven out of 66 (16.6%) single base-pair substitutions fell within RGYW/NRCY motifs. Among DLBCL, mutations were preferentially represented by single base-pair substitutions (n=81), whereas only 4 deletions and 2 insertions were observed. The transition/transversion ratio was 42/25 (1.68; expected 0.5; P<0.001). Twenty six out of 81 (32.1%) single base-pair substitutions fell within RGYW/NRCY motifs. Among PMBCL, one missense mutation affected PIM-1 exon 2 and three missense mutations in c-MYC exon 2 lead to aminoacid substitution with potential functional consequences.

Conclusions: The implications of our results are twofold: First, aberrant SHM is involved in the pathogenesis of PMBCL. Second, aberrant SHM targets both PMBCL and DLBCL. Since aberrant SHM has been advocated as a molecular marker of DLBCL, our results corroborate the notion that PMBCL represents a subtype of DLBCL rather than a distinct entity.

SOCS-1 MUTATIONS IN MEDIALSTINAL B-CELL LYMPHOMAS AND MEDIALSTINAL B-CELL LYMPHOMA CELL LINES

P. Möller1, I. Melzer1, C. Dorch1, O. Rütz1, S. Brüderlen1, F. Leithäuser1, M. Wengel2, M. Dyer2, T. F. E. Barth2

1University of Ulm, Institute of Pathology, Ulm, Germany; 2Leicester University, MRC Toxicology Unit, Leicester, UK

Introduction: The oncogenic pathway of primary mediastinal B-cell lymphoma (PMBL) is poorly understood. Cytogenetic studies and expression profiling revealed overrepresentation and overexpression of JAK2 as a causative oncogene, and JAK2 was found constitutively phosphorylated in the PMBL line, MedB-1.

Methods: We studied MedB-1 for phosphorylation status and turnover of JAK2 and downstream targets/interaction partners of JAK2 and performed DNA sequencing analysis of PMBL cell lines MedB-1 and Karpos 1106P and PMBL tumor tissues.

Results: In Med-B-1, JAK2, albeit phosphorylated, is not overexpressed, and protein turnover is critically delayed. This coincides with a biallelic mutation in the SOCS-1 gene which abrogates the SOCS-box function of SOCS-1. Ectopic expression of wtSOCS-1 lead to reduction of phospho-JAK2 and phospho-STATS, upregulation of RB1 and repression of cyclin D1, along with growth arrest. Further analysis revealed identical mutations in the parental tumor of MedB-1 and other transcriptionally relevant mutations of SOCS-1 in 9 of 20 PMBLs. Interestingly, Karpos 1106P has a biallelic large defect on 16p comprising the entire SOCS-1 locus.

Conclusions: We conclude that, in MedB-1, action of phospho-Jak2 is sustained due to defective SOCS-1. Hence, SOCS-1 qualifies as a novel tumor suppressor which, we found, is frequently mutated in PMBL and completely lost in Karpos 1106P.

MOLECULAR GENETIC CHARACTERIZATION OF THREE NOVEL VARIANT TRANSLATIONS OF THE (T11;18)(q21;q21) ASSOCIATED WITH EXTRANODAL MALT LYMPHOMAS

E. Murza Pena1, E. Celler-Bauchu1, K. Hina1, T. Zivkovic1, L. Billir1, M. Dubata1, H. Taguchi1, S. Gazz1, F. Berger1, G. Salle1, I. Miyoshi1, C. Bokemeyer1, J. Diezmann1

1Oncology and Hematology, University Hospital Hamburg-Eppendorf, Hamburg, Germany; 2Laboratory of Molecular Biology, Centre Hospitalier Lyon Sud, Lyon, France; 3Department of Hematology and Respiratory Medicine, Kochi Medical School, Kochi, Japan

Introduction: The (t11;18)(q21;q21) represents the most frequent aberration in extranodal MALT lymphomas and occurs in about one third of the cases. The t11;18 leads to a fusion of the API2 gene on chromosome 11 and the MLT/MALT1 gene on chromosome 18, coding for a chimeric protein that effectively activates the NF-κB transcription factor.

Methods and results: We herein describe three novel variant translocations of the (t11;18), the t11;18;13(q24;q22)(q21), the t11;12;18(q21;q12q21), and the t11;14;18(q21;q12q21), occurring in one MALT lymphoma of the stomach and two MALT lymphomas of the lungs, respectively. Conventionnal cytogenetic analysis revealed: 146;XY(0;18)(11;13)(q24;12q12)(q11;14;18)(q21;q12q21) [10]. 146;XY(11;12;18)(q21q12q21) [21] in the first case; 146;XY(11;12;18)(q21q12q21) [50] in the second case; and 46;XY(t11;14;18)(q21;q21q21)(23) in the third case. In all cases, fluorescence in situ hybridization (FISH) with API2 (PAC16G6) and MALT1/MALT1 (PAC9597) specific probes showed an API2-MALT1 fusion encoded on the der(11) as in the standard t11;18. Split hybridization signals of the API2 specific probe were located on the der(6), der(12), and der(14), indicating the presence of three-way-translocations. RT-PCR and DNA sequencing revealed an in-frame fusion of exon 7 of API2 and MALT1 in all three cases. The breakpoints within MALT1/MALT1 were determined as follows: exon 5 of the transcript variant 1 of MALT1/MALT1 in the t11;12;18, exon 5 of the transcript variant 2 of MALT1/MALT1 in the t11;14;18, and exon 8 of the transcript variant 1 of MALT1/MALT1 in the t11;18;11. Conclusion: We conclude that, similar to the standard t11;18, the new variant translocations t11;12;18, and t11;14;18, lead to the pathogenetically relevant 5'API2-3'MALT1/MALT1 fusion and that due to an additional translocation event the expression of the reciprocal MALT1/MALT1-API2 is excluded. Supported by grant 106092 (J.D.) from the Deutsche Krebshilfe.

MALT CONTAINS NUCLEAR EXPORT SIGNALS AND REGULATES CYTOPLASMIC LOCALIZATION OF BCL10

M. Nakaizawa, Y. Hosokawa, R. Suzuki, S. Tsuzuki, M. Seto

Division of Molecular Medicine, Aichi Cancer Center Research Institute, Nagoya, Japan

Introduction: A characteristic histopathological feature of mucosa-associ-ated lymphoid tissue (MALT) lymphomas with t(1;14) or t(11;18) is aberrant nuclear localization of BCL10 which localizes in the cytoplasm of normal lymphocyte. BCL10 and MALT1 as well as API2-MALT1 are key molecules in MALT lymphomagenesis. In an attempt to understand significance of biological and oncogenic roles of these molecules, mechanism of their subcellular localization was studied.

Methods: Expression vectors of full-length MALT1, various MALT1 mutants, full-length API2-MALT1 and full-length BCL10 were constructed. COS7 cells were transfected with these vectors and examined by immunofluorescence microscopy. Nuclear export signal (NES) specific
inhibitor, leptomycin B (LMB) was used to examine the mechanism of subcellular localization.

**Results:** Full-length MALT1 and full-length API2-MALT1 were localized in both nuclear and cytoplasm with LMB, while they were localized only in the cytoplasm without. The various MALT1 mutants revealed the cytoplasmic localization determining regions in the C-terminal of MALT1. When MALT1 mutants and BCL10 were both expressed, the both were localized in cytoplasm only although BCL10 alone is originally in both nucleus and cytoplasm.

**Conclusions:** MALT1 and API2-MALT1 contain nuclear export signal (NES) in the C-terminal region and are shuttling between nucleus and cytoplasm. MALT1 was involved in the nuclear export of BCL10. These results correlate well with the nuclear BCL10 expression pattern found in both t(1;14) and t(1;11;18) MALT lymphomas.

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**REDUCTION OF TREATMENT IN LOCALIZED INDOLENT PRIMARY GASTRIC LYMPHOMA (PGL): RESULTS OF TWO PROSPECTIVE STUDIES GIT NHL 01/92 + 02/96**

R. Liench1, W. Berdel1, N. Willich, G. Reinartz1, M. Tiemann1, P. Koch1 et al.

1Department of Haematology/Oncology, Radiation Oncology, University of Muenster, Muenster, Germany; 2Department of Haematopathology, University of Kiel, Kiel, Germany

**Introduction:** In study 01/92 we compared treatment results in primary gastrointestinal lymphoma after combined surgery (SCM) and conservative management (CM) only. There was no advantage for surgery in localized PGL (Koch, JCO 2001). Aims of study 02/96 were (1) to confirm these results and (2) to reduce treatment intensity in indolent PGL without compromising treatment results.

**Methods:** CM was stratified according to histologic grading, stage of disease, and the effect, whether surgery had been carried out or not. In the 01/92 study indolent PGL patients received an extended field (EF) radiation therapy (Rx) with total abdominal irradiation and additionally in stage II a T-field Rx and 6 cycles of COP. The dose was 30 Gy in the EP followed by a boost of 10 Gy (the latter omitted after complete resection) on sites of tumour (IF). In study 02/96 the radiation volume was reduced in stage II to total abdominal irradiation without the additional T-field and no chemotherapy and in stage I limited to the lower border of the Sth lumbar vertebra.

**Results:** Concerning the organ preserving CM the 2nd study confirmed the earlier results (Koch, Proc Asco 2001). With respect to treatment reduction, event free survival (EF), survival (S) and cause specific survival (CSS) were not compromised. In study 01/92 with 99 months median time of observation (MTO) for 51 patients (pts) EF, S, CSS is 96%, 91% and 94% respectively. Results of study 02/96 (145pts) after MTO of 12 months are comparable: EF 82%, S 90% and CSS 97%. There is no statistical difference between both studies.

**Conclusion:** Treatment intensity in indolent PGL can be reduced without compromising treatment results. As consequence a further reduction in Rx was introduced in our third study. Detailed data will be presented.

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**HIGH RELAPSE RATE IN PATIENTS WITH MALT-LYMPHOMA WARRANTS LIFE-LONG FOLLOW UP**

M. Raderer1, B. Streubel2, S. Wochner1, A. Puespock1, U. Jaeger1, M. Formanek1, A. Chott

1Internal Medicine I, University of Vienna, Vienna, Austria; 2Clinical Pathology, University of Vienna, Vienna, Austria; 3Internal Medicine IV, University of Vienna, Vienna, Austria; 4Otorhinolaryngology, University of Vienna, Vienna, Austria

**Introduction:** MALT lymphoma is thought to be an indolent disease, with a good prognosis following various forms of treatment. Little, however, is known about the rate and pattern of relapse following successful treatment.

**Patients and Methods:** We have analyzed time to and pattern of relapse in patients with MALT lymphoma, along with information of t(11;18)/q21q21), t(1;14)q22q32), t(4;18)(q32q21) involving IGH/MALT1, trisomy 3 and trisomy 18. Eighty-eight patients achieving complete remission (CR) after initial therapy with sufficient follow-up data were available. Primary site of disease was the stomach (n = 36), salivary gland (n = 20), ocular adnexa/orbit (n = 15), lung (n = 8), thyroid (n = 5), breast (n = 3), liver (n = 2) and skin (n = 1).

**Results:** Thirty-three patients (37%) relapsed between 16–307 months (median 47 months) after initial CR. Ten relapses were local, while the remaining patients relapsed in a distant organ. Eight of 36 gastric versus 25/50 non-gastric MALT lymphomas (P = 0.02) relapsed. Four patients had a second recurrence 26–56 months after a second CR. Relapse rates were not related to forms of initial treatment. Chromosomal aberrations were detected in 14/28 (50%) relapsing patients, and chromosomal alterations were identical at diagnosis and relapse, suggesting that MALT lymphomas do not acquire additional aberrations in the course of the disease. No significant association of any of the genetic changes investigated with relapse was found. Interestingly, patients with t(11;18)/q21q21) had a significantly longer median time to relapse (76 months) than patients without this translocation (29 months; P = 0.012). In addition, only one patient developed diffuse large B-cell lymphoma upon relapse, suggesting that the risk of transformation is minimal in MALT lymphoma.

**Conclusions:** In view of the late relapses seen in our series, life-long observation of all patients treated for MALT lymphoma appears to be required. However, in terms of genetics and risk of transformation, MALT lymphoma appears to be an extremely stable disease.

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**POPULATION BASED ASSESSMENT OF TREATMENT OUTCOMES FOR GASTRIC NON-HODGKINS LYMPHOMA**

S. Lyons1, P. Middleton, J. White1, A. Lenard2 et al.

1Haematology, The Royal Victoria Infirmary, Newcastle-Upon-Tyne, UK; 2SNLQ Office, Edinburgh University, EDINBURGH, UK

**Introduction:** Gastric lymphoma accounts for less than 5% of gastric malignancies. There is a lack of consensus over the best modality of treatment with surgery alone, chemotherapy alone and combination approaches all in common usage.

**Methods:** All cases of gastric lymphoma in Scotland and the North- ern region of England were prospectively studied. Patients were classified as high or low grade lymphoma depending on their Real or Kiel subtype. Follow up was for a median of 82.9 (high grade) and 73.4 months (low grade lymphoma).

**Results:** 235 patients were registered (126 male and 109 female): 167 high grade and 68 low grade lymphomas. The median age of the low grade lymphoma cohort was 66.5 (21–98) and 70 (22–91) for the high grade cohort. Increasing age was associated with poorer overall survival in both cohorts (log rank P = 0.0013 and P = 0.0002 respectively). Antibiotic therapy as first line therapy for low grade disease gave a significant survival advantage (P = 0.0003) as did combination surgery and chemotherapy for the high grade cohort (P = 0.0003). Survival was not significantly different when comparing surgery alone and chemotherapy alone for high grade disease (P = 0.2). In both groups the survival advantage of antibodies (in the low grade group) and surgery with chemother- apy (in the high grade group) remained highly significant throughout each age range examined.

**Conclusion:** The use of antibodies as first line therapy in low grade gas- tric lymphoma is associated with a superior survival advantage (independent of stage and age). Combination therapy with surgery and chemotherapy in our cohort of high grade disease patients has a significant survival advantage (independent of stage and age). This finding requires further investigation.

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**MUCOSA ASSOCIATED LYMPHOID TISSUE (MALT) LYMPHOMA: CHARACTERISTICS AND TREATMENT OUTCOME OF 195 CASES**

K. Reit, J. Yahalom2

1Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, USA; 2Lymphoma Disease Management Team, Memorial Sloan-Kettering Cancer Center, New York, USA

**Introduction:** Mucosal associated lymphoid tissue (MALT) lymphoma is the 3rd most common non-Hodgkin’s lymphoma. There is relatively limited information on the characteristics and outcome of these patients, thus this study sought to review the cases evaluated at our comprehensive cancer center over the past 20 years.
Methods: 195 cases of MALT lymphoma that were pathologically confirmed at our center were identified. We retrospectively reviewed the clinical information.

Results: There were 86 (44%) men and 109 (56%) women with a median age of 61 years (range 24–90). The stomach was the most common primary site with 93 (48%) cases. Other primary sites included lung (19 cases), ovary (16 cases), skin (14 cases), salivary gland (9 cases), subcutaneous tissue (8 cases), conjunctiva (6 cases), thyroid (5 cases), oral cavity (5 cases), breast (5 cases), other GI sites (5 cases), and other sites (12 cases) including the bladder, nasopharynx, cerebrospine angle, kidney, duodenum, and base of skull. Patients were likely to present with an early stage with 144 (74%) presenting with stage I disease, 9 (5%) with stage II disease, 1 (1%) with stage III, 32 (16%) with stage IV, 63 (32%) with recurrent disease, and 3 (2%) with an unclear stage. 130 patients were treated with radiation therapy (RT) alone with a median dose of 3000 cGy. 18 patients were treated with chemotherapy (CTX) alone which usually consisted of CHOP (+/- Rituxan). 7 patients received a combination of CTX and RT, and 12 patients were observed rather than treated. The median follow-up was 30 months (range 2–205). There was a 94% 5-year overall survival and a 99% 5-year cause-specific survival. Patients with stage I and II disease who were treated with RT alone had a 95% 5-year freedom-from-treatment failure.

Conclusions: This is one of the largest series of MALT lymphoma patients with a wide distribution of primary sites and complete treatment outcome information. We document an excellent outcome for patients with early stage disease treated with radiation therapy alone and an overall very encouraging prognosis for the group as a whole.

NON SURGICAL TREATMENT FOR LOCALIZED GASTRIC MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) LYMPHOMA: PRELIMINARY RESULTS OF A MULTICENTER PROSPECTIVE STUDY IN JAPAN

1Department of Gastroenterology, Aichi Cancer Center Hospital (ACCH), Nagoya, Japan; 2Department of Pathology and Molecular Diagnostics, ACCH, Nagoya, Japan; 3Department of Pathology, Okayama University, Okayama, Japan; 4Department of Endoscopy, National Cancer Center Hospital, Toyama, Japan; 5The Third Department of Internal Medicine, Toyama Medical and Pharmaceutical University, Toyama, Japan; 6Statistics and Cancer Control Division, National Cancer Center Research Institute, Tokyo, Japan

Introduction: Although eradication of Helicobacter pylori (HP) and radiation therapy (RT) have curative potential for gastric MALT lymphoma (G-MALT), no prospective study has yet been reported. This prospective study evaluated the efficacy and safety of this non-surgical treatment for localized G-MALT. The primary endpoint was failure-free survival (FFS).

Methods: Eligibility criteria were histologically proven G-MALT, stage I-II, age 20–75 years, PS 0–1, no prior therapy, adequate organ function, and written informed consent. Patients received HP eradication therapy (ET) consisting of a PPI-based triple regimen, and RT of 30 Gy in cases of persistent or recurrent disease after ET.

Results: Between 01/2001 and 12/2003, 150 patients were registered and 149 were included in the preliminary analysis. Of these, 18 (12%) were ineligible: 16 by central pathological review and two for other reasons. Baseline characteristics of the 131 eligible patients were: median age of 60.5 (35–75); male/female =49/82; stage I-II = 126/5; HP +/- = 107/24; depth of invasion within/beyond the submucosa, 118/13. ET was administered completely to all patients. Twenty-nine patients (22%) underwent RT due to persistent or recurrent disease after ET and 25 (92.6%) of these achieved complete remission with RT. No hemorrhage or perforation of the stomach were observed. With a median follow-up of 31.2 months, six events were considered 'treatment failures': death not related to the treatment, 1: salvage gastrectomy, 1: transformation to diffuse large B-cell lymphoma, 3: and development to stage IV, 1. Two-year FFS and overall survival were 96.7% and 99.2%, respectively.

Conclusion: This organ-preserving treatment for localized G-MALT is safe and effective. It has the potential to become the standard treatment for this disease, although long-term follow up is necessary.

VALIDATION OF THE GELA SCORING SYSTEM FOR EVALUATING GASTRIC BIOPSIES FROM PATIENTS WITH MALT LYMPHOMA FOLLOWING ERADICATION OF HELICOBACTER PYLORI

C. Cosio-Bergami1, C. Capell1, T. Motta1, E. Pedrinisi1, S. Pileri1, M. Ponzi2, F. Bertoni2, A. Conconi2, E. Zucca3, A. Wotherspoon4
1Département de Pathologie, Hopital Henri Mondor, Paris Créteil, France; 2Ospedale di Circolo, Fondazione Macchi, Varese, Italy; 3Ospedali Riuniti di Bergamo, Bergamo, Italy; 4Istituto Cantonale di Patologia, Locarno, Switzerland; 5Polliclinico Santa Orsola, Bologna, Italy; 6Ospedale San Raffaele, Milano, Italy; 7Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; 8Az. Ospedaliera "Maggiore della Carità", Novara, Italy; 9The Royal Marsden Hospital, London, UK

Introduction: Assessment of gastric biopsies in patients with MALT lymphoma following eradication of Helicobacter pylori (Hp) is a major factor in determining subsequent management. In general, schemes for reporting the histological features in these biopsies have been unreliable and unpredictable. The GELA system provides a simple method for analysis and reporting post-eradication gastric biopsies. The aim of this study was to validate the application and reproducibility of this scheme in a group of Histopathologists previously unfamiliar with the system.

Methods: A total of 161 biopsy sets from 22 MALT lymphoma patients previously treated by Helicobacter eradication therapy (range 3–11 biopsy sets per patient) were examined independently by seven pathologists five of whom had never previously used the GELA system.

Results: There was complete agreement by all pathologists in 66 biopsies (41%). There was disagreement by 1, 2, or 3 pathologists in 43, 30 and 22 (7.5%, 18.5% and 13.5%) respectively. In only 6 cases were more than two different scores given on a single biopsy. The majority (64%) of non-concordant responses was present across the border of complete remission (CR) and probable minimal residual disease (pMRD).

Conclusions: The GELA system for evaluating gastric biopsies from patients with MALT lymphoma treated by Hp eradication is reproducible and simple to use. The area of greatest difficulty is the border between CR and pMRD, a distinction that is of minimal clinical significance.

WOTHERSPoon CRITERIA COMBINED WITH B-CELL CLONALITY ANALYSIS BY ADVANCED PCR TECHNOLOGY DISTINGUISHES CRYPTIC GASTRIC MARGINAL ZONE B-CELL LYMPHOMA FROM CHRONIC GASTRITIS

T. F. E. Barth, on behalf of the German Reference Centers and St. Gallen Reference Center for Lymphome Pathology

University of Ulm, Institute of Pathology, Ulm, Germany

Introduction: Gastric marginal zone B-cell lymphoma of MALT-type is a morphologically well defined lymphoma yet quite often impossible to be distinguished from severe chronic gastritis on morphological grounds alone. Clonality of the immunoglobulin (Ig) heavy chain (H) genes detected by PCR was suggested as a decisive criteria. However, there is controversy whether B-cell clonality also exists in chronic gastritis.

Methods: An expert panel re-examined the histology and immunohistochemistry of a total of 97 cases of gastric biopsies including clear-cut marginal zone lymphoma, chronic gastritis and ambiguous cases, by applying the Wotherspoon criteria on the basis of hematoxylin and eosin and CD20 standard diagnostic stainings. An advanced PCR system for detection of clonal IgH gene rearrangements was independently applied in two institutions on each case.

Results: Overt lymphoma (Wotherspoon score 5) was clonal in 24/26 cases. Chronic gastritis (Wotherspoon 1 and 2) was not clonal in 52/53 cases, the clonal case being Wotherspoon 2. Of 18 cases with ambiguous histology (Wotherspoon 3 and 4) four were clonal. None were clonal in the 31 cases of atrophic gastritis.

Conclusions: Using advanced PCR technology, clonal gastritis is extremely rare if at all existent. Thus, B-cell clonality in Wotherspoon 3 and 4 cases is regarded as suitable to finally establish the diagnosis of gastric marginal zone B-cell lymphoma.
Mast Cells and Eosinophils as Prognostic Factors in Malignant Lymphoma

Introduction: Malignant lymphoma (MCL) is an aggressive lymphoma and although disease heterogeneity exists, it is generally characterized by poor prognosis. This makes it difficult but highly necessary to identify prognostic markers. A high proliferative index, demonstrated by gene expression profiling and Ki-67 staining has been previously correlated with worse survival. In recent years, in some types of cancer, mast cells have been suggested to work in favor of carcinogenesis. CCL3, a chemokine attracting mast cells, has been shown to be over-expressed in MCL. Moreover, eosinophils have an anti-tumor effect in non-lymphomatous cancers but are associated with poor prognosis in Hodgkin lymphoma (HL). We set out to determine the prognostic impact of the number of mast cells, eosinophils and Ki-67+ cells in MCL tumors. We also wished to evaluate if digital image analysis could be substituted for manual cell counting, which may be useful in the future for automating and increasing the reproducibility of such studies.

Methods: Biopsies from 40 patients diagnosed with MCL were immunohistochemically stained with an antibody against tryptase (a mast cell specific protein) and with an antibody against Ki-67, to detect cycling cells. Haematoxylin-eosin staining was used to visualise eosinophils. Mast cells, eosinophils and Ki-67+ cells were counted manually and by computerised image analysis. The median percentage of Ki-67+ cells in this material was 23%, and MCLs were classified as having a high or low proliferation index according to this border. Clinical parameters were assessed by reviewing hospital files of the patients.

Results: In this study, stage III-IV (55%), presence of B-symptom, systemic disease, bone marrow infiltration, and high age predicted poor prognosis. Eosinophil infiltration and Ki-67 index correlated with worse overall survival (P = 0.006 and P = 0.02 respectively). Patients with high numbers of infiltrating mast cells showed a tendency to have poorer survival (P = 0.051). Comparing the difference between manual and computerised counting, 34 of 40 cases gave the same grouping.

Conclusions: Similar to HL, eosinophils and mast cells have a negative prognostic impact in MCL and Ki-67 staining confirmed as an adverse prognostic marker. The use of image analysis for these purposes is promising but requires further refinement before it could substitute manual counting. It will be interesting to evaluate these markers in a larger cohort, which is currently underway, and also to investigate the biological significance.

High Rates of Failure-Free Survival (FFS) and Overall Survival (OS) in Untreated Malignant Cell Lymphom (MCL) after Rituximab Plus HyperCVAD-R (R-CVAD) Alternating with Rituximab Plus HyperCVAD (R-M) Adriamycin Methotrexate-Cytarabine

Introduction: MCL has a poor prognosis with current management. R-HCVAD (considered one cycle) alternating q 21 days with R-MA (considered another cycle) as described earlier (Ann Oncol. 13, suppl 2, 2002 #24). Prophylaxis with mesna, calcium leucovorin, pre-dnisone eye drops, G-CSF, antibacterial, antifungal, and antiviral therapy. Results: 97 patients evaluable for analysis of response, survival and toxicity. 87% complete response (CR). Of 60/4 (median follow up 40 months), the 3-year FFS and OS are 67% and 81%, respectively. Adverse factors for FFS are b2 microglobulin >2 mg/L (p = 0.002), Age >65 years (p = 0.009), and LDH >normal (p = 0.01). Patients >65 years have similar FFS regardless of pre-treatment levels of B2microglobulin. Grade 4 hematologic toxicity was significant. Five patients died during treatment of sepsis (3), pulmonary hemorrhage (1), and unknown cause (1). Four patients developed myelodysplasia/acute myelogenous leukemia after treatment and while in CR and three have died, for a total of 8 deaths in the study (8%).

Conclusion: R-HCVAD alternating with R-MA is highly effective in untreated MCL. Toxicity is as expected for an intense regimen. An update of FFS will be presented at the meeting.

A Randomised Phase II Study of Fludarabine/Cyclophosphamide + Rituximab in Patients with Untreated Mantle Cell Lymphoma

Introduction: Mantle cell lymphoma (MCL) is a poor prognosis sub-type of B-cell NHL with a 30% five year survival. There is no current curative or generally recommended initial treatment. The combination of fludara-bine and cyclophosphamide (FC) has produced a high rate of durable responses in small studies. MCL is a strongly CD20 positive tumour, so using rituximab in combination with chemotherapy may improve outcomes. This randomised phase II trial was designed to assess the response rates for the FC combination +/- rituximab, prior to a planned randomised phase III trial with overall survival as the primary endpoint.

Patients and Methods: Eligible patients aged ≥18 years, with histologically proven diagnosis of MCL were randomised to either FC or FC plus rituxi-mab (FCR). The regimen was given as oral F 40 mg/m2 day 1–3 and C 250 mg/m2 day 1–3 plus R 375 mg/m2 day 1 iv in the FCR arm. (Alternatively F 25 mg/m2 day 1–3 and C 250 mg/m2 day 1–3) Cycles were repeated every 28 days with reassessment of disease status made after 4 cycles. If complete or partial remission was attained, patients proceeded to a maximum of 8 cycles of treatment. If there was no response or progressive disease, patients were taken off study.

Results: Between September 2002 and February 2004, 83 patients have been randomised (42 FC, 41 FCR). Patient characteristics are well matched between the two arms: median age 64 years, 77% male, 90% ECOG 0–1, 87% stage III/IV. The number of cycles of treatment is similar in both arms with 89% patients having received at least 4 courses of chemotherapy. Initial (after 4 courses of chemotherapy) overall response rates are 93% in both arms with complete response rates of 40% and 44% for the FC arm and FCR arm respectively. At median 4 months follow up, progression free survival is 83% in FC arm and 81% in FCR arm. Overall survival is 90% in FC arm and 83% in FCR arm. Toxicity in both arms is similar and acceptable.

Conclusions: Preliminary analysis of FC +/- rituximab demonstrates response rates comparable to previous published data for other regimens, suggesting this may be a suitable treatment for patients with untreated MCL. Whether either arms of the trial could become standard treatment for MCL requires further long-term analysis allowing assessment of progression free and overall survival as in the planned phase III trial.

Autologous Stem Cell Transplantation (ASCT) in First Remission for Patients with Malignant Cell Lymphoma is Associated with a Prolonged Survival

Introduction: MCL and other indolent and marginal zone B-cell lymphomas are characterized by indolent clinical courses and subsequent progression to aggressive disease. Both autologous and allogeneic transplantation can result in prolonged complete remissions and survival. However, the role of ASCT in the treatment of MCL remains controversial. The purpose of the present study was to re-evaluate the role of ASCT in untreated MCL patients in first remission. Methods: A retrospective chart review of all MCL patients undergoing ASCT at Mayo Clinic Rochester and University of Rochester Medical Center between 1993 and 2007 was performed. Results: A total of 46 patients met inclusion criteria. There were no significant differences with regard to demographic features and disease characteristics between the two groups. The median follow-up time was 50 months (range 9 months–19 years) and from ASCT was 26.7 months (range 3 months–7 years).
Nineteen pts underwent BM in first CR/PR and 22 pts in second or greater remission. On univariate analysis (age, gender, stage, PS, IPPI, BM) in 1st CR vs later and number of chemotherapy regimens the only factors which were significant were number of chemotherapy regimens prior to ASCT and ASCT in first remission vs. >first remission. Median overall survival (OS) from ASCT for the patients in first remission has not yet been reached and for the patients beyond first remission was 35.6 months (P=0.0001). Median progression free survival (PFS) from ASCT was 52.9 months for the patients transplanted in first remission vs. 22.5 months (P=0.06) for the pts transplanted beyond first remission. Disease status at transplant appears to be the most significant factor affecting survival; therefore for pts in whom ASCT is being considered it is advisable to proceed early in the disease (first remission) and not wait for relapse.

CHOP AND DHAP PLUS RITUXIMAB FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN MANTLE CELL LYMPHOMA (MCL): A STUDY FROM THE GELA

R. Delaunay1, C. Haouzi1, V. Levy2, V. Ribrag3, P. Brice4, H. Tilli5, C. Salanoubat1, A. Delmi1, A. Van Hoof6, O. Casassona7, F. Lefere8, G. Suiesse9, N. Bessede9, O. Hermitte9

1Laboratoire d'Immunologie, GELA, Paris, France; 2Biostatistiques, GELA, Paris, France; 3Anatomie Pathologique, GELA, Paris, France

Introduction: The aim of this study is to confirm in a multicentric study the efficacy of an induction regimen with high dose AraC and consolidation with ASCT in responding patients, and 2) to investigate the impact of Rituximab in the setting of this intensive treatment in younger patients with MCL.

Methods: Patients under 66 years with histologically proven, stage III/IV MCL were included. Treatment consisted of two courses of CHOP, one R-CHOP and three R-DHAP. Peripheral blood stem cells harvest was performed at the end of the third R-DHAP. Responding pts were eligible for an ASCT after high dose therapy with TBI (10 Gy), AraCytine (G/m²) and Melphalan (140/m²) (TAM 6) or BEAM if TBI could not be performed.

Results: From May 2000 to September 2003, 52 pts were included. Median age was 56 years. Characteristics of patients are as follows: bone marrow involvement 87%, leukemia disease 52%, gastrointestinal involvement 50%, PS=1 18%, LDH >10x normal. Fifty-one pts are evaluable after the three courses of (R)-CHOP. Response rates were as follow: CR 12%, PR 30% and PD/SD 58%. Forty-nine pts have completed the three courses of R-DHAP. After the R-DHAP, response rates were: PR 37%, CR 55% and PD/SD 8%. PBSC harvest was successful in all but one. Forty-three pts were autografted with a TAM 6 (37 pts) or with a BEAM (5 pts) or high dose Melphalan (1 pt). After ASCT, all patients but two (95%) were in CR. Median follow-up of 40 months, EFS is 64% and OS is 86%

Conclusion: This study confirm that intensive regimens with high dose AraC and consolidation with ASCT for responding pts is feasible in a multicentric setting with prolonged EFS and OS in untreated MCL. The impact of Rituximab is still unclear and further follow-up is warranted. Multicentric European study is currently ongoing to test this approach against R-CHOP followed by ASCT.

A PHASE II STUDY OF YTTRIUM 90 (90Y) IBRITUMOMAB TIUXETAN (ZEVALIN) FOR TREATMENT OF PATIENTS WITH RELAPSED AND REFRACTORY MANTLE CELL LYMPHOMA (MCL)

A. Young1, M. Rodriguez, B. Pro, P. McLaughlin, J. Romaguera, F. Hagemeister, M. Wang

Lymphoma/Myeloma, M. D. Anderson Cancer Center, Houston, TX, USA

Background: Although recent studies have shown the clinical utility of yttrium 90 ibritumomab tiuxetan(Zevalin) in relapsed and transformed indolent B-cell lymphoma, the clinical efficacy of zevalin in patients with MCL is unknown.

Patients and Methods: Patients with relapsed or refractory MCL with measurable disease, age ≥ 18 years, and performance status ≤ 2 were eligible. Patients were required to have adequate function of the bone marrow, liver, and kidneys. Patients were excluded if they had prior stem cell transplantation, CNS lymphoma, HIV infection, pleural effusion, HAMA reactivity, or circulating lymphoma cell count >5000/mm³. Patients with pretreatment platelet count ≥150,000/mm³ received a dose of Zevalin at 0.4 mCi/kg (maximum dose 32 mCi), whereas those with platelet count <150,000/mm³ received 0.3 mCi/kg.

Results: Twenty patients were enrolled, of whom 17 are evaluable for treatment response and toxicity. The median age was 66 years (range 51–77). The median number of prior regimens was 3 (range 1–6). Ten patients were previously treated with Hyper-CVAD alternating with MTX/Ara-C. Zevalin treatment was generally well tolerated, with the most common toxicities being hematologic. Objective responses were observed in 7 patients (41%), including 3 CR, 2 CRu and 2 PRs. Two additional patients had stable disease.

Response rate was higher in patients who had had 1 or 2 prior regimens than in patients with 3 or more prior regimens. Median progression free survival for entire group was 9 months (range 4 + 19 + months).

Conclusion: The observed responses to Zevalin in heavily pretreated patients with MCL are promising and warrant further investigation of its activity after first or second relapse, and in conjunction with front-line therapy.

A PREDICTIVE MODEL FOR LIMITED STAGE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): A RETROSPECTIVE ANALYSIS OF 1,352 CASES PERFORMED BY THE INTER-GRAUPO ITALIANO LINFOMI (III)

S. Cortellazzi1, S. Laminari1, M. Belfi1, M. Martelli1, U. Violo1, L. Rigacci1, A. Ambrosetti1, E. Pogliani2, T. Chiesi3, G. Rossi4, A. Rossi4, T. Barbui5, M. Brugali5, M. Federico5, E. Migliaccio, Ospedali Riuniti, Bergamo, Bergamo, Italy; 2Dept. Oncology and Hematology, University of Modena and Reggio Emilia, Modena, Italy; 3U.O.A. Ematologia, Az. Ospedaliera S. Giovanni Battista, Torino, Italy

Introduction: few studies have explored the usefulness of a prognostic index specifically devised for patients with localized DLBCL. The IIL has performed a retrospective analysis of a large group of patients with limited stage DLBCL and developed a new prognostic model.

Results: 1,352 patients with localized (Ann Arbor stage I-II) aggressive B-cell lymphoma (IWF: G or H, WHO:DLBCL) diagnosed from 1988 to 2002 and without CNS involvement were identified. Median age was 57 yrs (range 17–91) and M/F ratio was 1.26. Clinical stage was I in 19%, II in 34%, II in 28% and III in 28% patients, respectively. Extranodal involvement was present in 53%, 7% had >1 extranodal site, 26% had Bulky disease (≥10 cm), 28% elevated LDH, 19% B2M, 38% ESR>30, 21% reduced albumin (<3.5 g/dL). Patients were treated with ADM-containing regimens in 18% and RT. The median follow-up was 62 months and 5-year OS was 71%. By univariate analysis 11 variables were found to be predictive of short survival (P<0.01) (age, stage, number of nodal sites, PS, B symptoms, bulky, ES, ESR, LDH, RT, B2M and albumin). By Cox multivariate analysis, age ≥65 years (P<0.001), stage II nodal (P<0.001), high LDH (P<0.001) and bulky (P<0.01) were independent risk factors (RF). The prognostic model was validated with the sum of scores associated to each variable; advanced age, advanced stage, high LDH, and Bulky had a score 2; Stage a score of 1 was considered for stage Ie-IIe and 2 for stage II nodal. Three groups of patients with a different survival (P<0.000001) were identified: Patients at low (Score 0–1; 387 pts), intermediate (Score 2–3; 484 pts) or high risk (Score 4–8; 381 pts) had a 5 years OS of 87%, 77%, 51% respectively. The predictive performance of the model was internally validated through a non parametric Bootstrap method and through residuals analysis.

Conclusion: This prognostic model will allow us to better select appropriate therapeutic approaches for patients at different risks.

SUPERIORITY OF CHEMOTHERAPY ALONE WITH ALCBPV OVER THREE CYCLES OF CHOP PLUS RADIOTHERAPY FOR LOCALIZED AGGRESSIVE LYMPHOMA: FINAL ANALYSIS OF THE LNH 93-1 GELA STUDY


For the GELA, CHU Henri Mondor, Créteil, France
Introduction: Chemoradiotherapy is standard treatment for localized aggressive lymphoma. Because published series are heterogeneous with regard to prognostic factors, we aimed to determine the optimal therapy for young adults with low-risk localized lymphoma.

Methods: From March 1993 to June 2006, 647 patients (pts) under 60 years of age with aggressive lymphoma and without any adverse factor of the age-adjusted International Prognostic Index were randomly assigned to a chemoradiotherapy arm (329 pts) consisting of 3 cycles of CHOP (doxorubicin 75 mg/m²/day 1, cyclophosphamide 1.2 g/m²/day 1, vincristine 2 mg/m² days 1 and 5, bleomycin 10 mg days 1 and 5, prednisone 60 mg/m²/day 1 to 5) given every 2 weeks followed by sequential consolidation (methotrexate, ifosfamide, VP16, cytarabine).

Results: Principal characteristics were: median age, 47y; stage I, 67%; bulky disease, 11%; extranodal involvement, 50%; diffuse large B-cell histology, 83%. A 93% response rate was found in both arms. On an intent-to-treat basis and with a median follow-up of 7.7 y, pts treated with chemotherapy alone showed a significantly higher 5-year-event-free survival (EFS) and OS rate than pts treated with the chemoradiotherapy arm (92% vs 74%, respectively) as well as a higher 5-year overall survival (OS) rate with 90% vs 81%, respectively (P < 0.001). In a multivariate analysis, EFS and OS were affected by treatment arm, independently of stage and tumor burden.

Conclusion: We conclude that chemotherapy alone with the ACVBP regimen is superior to 3 cycles of CHOP plus radiotherapy for the treatment of low-risk localized aggressive lymphoma in pts under 60y.

IN Involved Field Radiotherapy in Partial Response After Doxorubicin-Based Chemotherapy for Advanced Aggressive Non-Hodgkin’s Lymphoma

E. Mosel, N. Noordik, J. Klein-Nelemans et al.

Radiotherapy, Leiden University Medical Center, Leiden, Netherlands;
Haematology, University Medical Center Groningen, Groningen, Netherlands

Introduction: When a partial remission (PR) is reached in patients with advanced aggressive non-Hodgkin’s lymphoma (NHL) after 8 cycles of doxorubicin-based chemotherapy (CT), the question arises if optimal salvage should consist of involved field radiotherapy (IF-RT) or high dose therapy (HD). As preparative study for a randomized trial, we analyzed in retrospect the impact on survival of IF-RT in case of PR after 8 cycles of CT given in 4 EORTC-trials.

Methods: From 1980 through 1999, 227 out of 974 primary treated patients with advanced aggressive NHL obtained a 50–99% response with a non-bone marrow after 8 cycles of CT. Although IF-RT was prescribed in case of PR in the EORTC protocols, only 164 were irradiated, 15 received HD, 4 were operated and 44 received salvage CT. Overall (OS) and progression-free survival (PFS) were estimated by the Kaplan-Meier method and outcomes were compared in IF-RT patients vs. no IF-RT patients (log-rank test). Balance for other risk factors (International Prognostic Index (IPI), histology, tumor size, stage, location of disease, given HD and first line CT type) was assessed using Fischer exact test. Finally, the two patient groups were compared in a multivariate analysis (Cox proportional-hazards model), that allowed adjustment for previous risk factors.

Results: The median follow-up of partial responders was 6.8 years (range 0.7–19.9). The median PFS was 4.8 years, and respectively 42.2% and 30.5% remained progression-free at 5 and 10 years. IF-RT was more frequently (P = 0.003) given in earlier trials. At start of treatment, LDH was more often raised (P = 0.001) and bone marrow more frequently involved (P = 0.02) in the non-irradiated group, resulting in a higher IPI risk profile. Bulky disease (>5 cm) was also more frequent in the non-irradiated group (P = 0.01). Nevertheless, analyses showed OS (P = 0.03) and PFS (P = 0.001) benefit of IF-RT in all patients, also per separate IPI group and in case of bulky disease. On multivariate analysis, IF-RT was the most significant factor affecting both OS (P = 0.02, HR 0.58) and PFS (P < 0.001, HR 0.48).

Conclusions: This retrospective analysis demonstrates that involved-field radiotherapy is effective for patients with a PR after doxorubicin-based chemotherapy; assessment of this salvage regimen in a randomized trial (compared to HD) seems justified.

CENTROBLASTIC (CB) AND IMMUNOBLASTIC (IB) SUBTYPES OF DIFFUSE LARGE B CELL LYMPHOMAS (DLBCL) HAVE SUCH A DIFFERENT CLINICAL OUTCOME THAT SHOULD BE CONSIDERED AS SEPARATE ENTITIES IN THE WHO CLASSIFICATION OF LYMPHOMAS. A GILS STUDY


1 Dipartimento di Oncologia ed Ematologia, University of Modena and Reggio Emilia, Modena, Italy; 2 Clinica Medica, Universita dell’Aquila, Teramo, Teramo, Italy; 3 Oncologia, A.O. “A. Pugliese Ciaocci”, Catanzaro, Italy; 4 Ematologia, Acquaviva dell’Forte, Italy

Introduction: The recent WHO classification on Tumors of the Haematopoietic and Lymphoid Tissues recognizes more than 35 different entities, with a frequency ranging from less than 2% to more than 30% for the category of DLBCL. However, this latter category seem to many clinicians too wide, including at least the two distinct subtypes of CB and IB.

Methods: Cases of DLBCL enrolled into prospective GILS clinical trials from 1988 and 2003 for whom a cytologic sub-classification (CB or IB) was available were identified and analyzed for investigating the impact of cytology on clinical outcome. The diagnosis was established on the basis of standard staining.

Results: Among 950 cases with DLBCL treated with slightly different ProMACE-CytaBOM derived regimens, 635 (67%) were classified as CB diffuse and 153 (16%) as IB lymphomas. Median follow-up for the whole series was 47 months. Univariate analysis for OS showed that advanced stage, age >60 years, B symptoms, elevated LDH, bulky disease, involvement of more than 1 extranodal site, low Lh levels and cytology had a significant impact in predicting a poorer outcome. In particular, patients with B cell DLBCL had a better 5-year OS than IB patients (74% vs. 43%, respectively, P < 0.001). The prognostic role of cytology was further confirmed by a multivariate analysis stratified by age which identified elevated LDH, low Lh levels, advanced stage and cytology as independent prognostic factors. Finally, the prognostic role of cytologic type was confirmed also in patients with similar IPI score.

Conclusions: In accordance with findings achieved by studies on gene expression profiling, patients with CB and IB DLBCL have a different prognosis. However, our approach is highly reproducible worldwide and incredibly cheap. The difference in outcome are so impressive that a classification in two distinct categories should be considered.

SURVIVIN IN DIFFUSE LARGE B CELL LYMPHOMA: EVALUATION AS A PROGNOSTIC MARKER


The Departments of Pathology & Haematology, The University of Newcastle-upon-Tyne, Newcastle-upon-Tyne, UK

Diffuse large cell lymphoma (DLBCL) is a high-grade neoplasm with variable prognosis. DLBCL is one of the most common types of lymphoma encountered and comprises about 20% of all non-Hodgkin's lymphomas. Presently few markers of prognosis which may aid disease management have been identified in DLBCL.

A series of 149 DLBCL were examined for nuclear over expression of Survivin which was shown to be an indicator of poor clinical prognosis. This association was evident when simply relating staining intensity to survival (P = 0.0196) and further strengthened when a composite score taking into account both staining intensity and the proportion of expressing tumour cells (P = 0.0101). In this latter instance median patient survival time was reduced from 37 to only 14 months. Further analysis of survival data indicated that over expression of both Survivin and Bcl-2 within the same tumour proved to be an even more powerful indicator of poor prognosis than Bcl-2 alone.

In conclusion expression of both IAP Survivin and Bcl-2 within the same tumour provided an extremely powerful indicator of poor clinical outcome and rapid decline. Therefore we suggest that IAP-Survivin over-expression should join over-expression of CD20, Bcl-2 and Germinal Centre Cell (GCC) phenotype together as an immunocytochemical phenotype that is indicative of poor clinical prognosis, thus strengthening the IPI as a means of managing these difficult patients.
CHARACTERISTICS AND OUTCOME OF DIFFUSE LARGE B-CELL LYMPHOMA IN HVC-POSITIVE PATIENTS IN LNH 9/3/98 GELA PROGRAMS

C. Besson1, D. Canonii, E. Lepage1, H. Tilly2, P. Gaulard2, B. Coiffier2, C. Gisselbrech1, F. Reyel1, O. Herment et al.
1Hématologie biologique, Hôpital de Bièvre, France; 2Service d’anatomopathologie, Hôpital Necker, France; 3Informatique médicale, Hôpital Henri Mondor, France; 4Hôpital Henri Mondor, France; 5Service onco-hématologie, Centre Henri Bucqerelle, Rouen, France; 6Département de pathologie, Hôpital Henri Mondor, France; 7Hématologie-oncologie, Centre Hospitalier Lyon Sud, France; 8Onco-hématologie, Hôpital Saint-Louis, France; 9Service hémato-oncologie, Hôpital Necker, France; 10Service d’hémato-oncologie adultes, Hôpital Necker, Henri Mondor, France; 11Service d’hémato-oncologie.

Epidemiological studies show a link between hepatitis C virus (HCV) and B-cell non-Hodgkin’s lymphoma (NHL). We studied the HCV-positive patients with B-cell diffuse large cell lymphoma (DLCL) included in the GELA programs. LNH93 and LNH 98. They were compared with the other patients with DLCL in the GELA programs included in these programs. HCV infection prevalence was 0.5% (26 out of 5586 patients). Histological review of HCV-positive DLCL were more frequent transformed from low-grade lymphoma than DLCL in HCV-negative patients (32% versus 6%, P = 0.02). This is also supported by a more frequent spleen involvement in HCV-positive patients (46% versus 17%, P = 0.001). HCV-positive patients had more frequently elevated LDH levels than other patients (77% versus 55%, P = 0.02). Although not reaching statistical significance, outcome of HCV-positive patients was poorer both for overall survival and event-free survival (P = 0.06) and for event-free survival (P = 0.16). At matching on age and prognosis factors, 2 years of follow-up, the overall survival was 56% (CI 0.33–0.76) among HCV-positive patients versus 80% (CI 0.70–0.89) and the event-free survival was 53% (CI 0.33–0.72) versus 74% (CI 0.64–0.84). The short term hepatic toxicity of chemotherapy was strongly increased among HCV-positive patients. The overall proportion of patients with hepatic toxicity was 67% and increased from 25% of patients after the first cycle to 45% after the fourth cycle of chemotherapy. It led to 4 hospitalizations and 1 toxic death. In conclusion, HCV-positive patients with DLCL differ from other patients both at presentation and during treatment. Specific protocols evaluating antiviral therapy should be designed for these patients.

RITUXIMAB AS A “CHEMO-EQUALIZER” IN THE MINT (MABTHERA INTERNATIONAL TRAIL GROUP) STUDY: TREATMENT RESULTS OF CHOP-21, CHOP-21, MACROB-21 AND PMiNECERO WITH AND WITHOUT RITUXIMAB IN YOUNG GOOD-PROGNOSIS PATIENTS WITH AGGRESSIVE LYMPHOMAS

1Internal Medicine I, Saarland University Medical School, Homburg, Germany; 2Mabithe International Trial Group, Saarland University Medical School, Germany; 3MUSE, Leipzig University, Leipzig, Germany.

Background: The addition of rituximab (R) to 6 cycles of CHOP-like regimens in the MINT trial significantly improved overall results and set a new standard in young good-prognosis patients with DLBCL. (Blood 2004;104:48a).

Objective: ACHOP-21 had been shown to be superior to CHOP-21 without R (NH-L1-B1 trial; Blood 2004; 104:626); we investigated whether these differences could be confirmed in the MINT trial where participating countries selected i of 4 CHOP-like regimens.

Methods: Intent-to-treat analysis of the primary endpoint time-to-treatment failure (TTF) and the secondary endpoints complete remission (CR) rate and overall survival (OS) of different regimens with or without rituximab.

Results: Of 823 evaluable patients, 48% (197/199) were randomized to CHOP-21 ± R (44% [180/181] to CHOP ± R, 4% [17/17] to MACROB-21 ± R and 4% to 16/16) PMiNECEBO. All regimens were well balanced for prognostic factors, except for MACROB-21 ± R with more favorable patients. Numbers for MACROB-21 and PMiNECEBO are too small for meaningful comparisons. CHOP ± R was better than CHOP-21 with respect to 2 year OS (75% vs. 62%; P = 0.02) and 2 year TTF (65% vs. 55%; P = 0.04), but not overall survival (86% vs. 83%; P = 0.67), confirming the results of the NHL-B1 trial. Rituximab significantly improved efficacy of CHOP (2-year TTF 55% vs. 43% and CHOP-21 (65% vs. 80%), and there were no more differences between R-CHOP and R-CHOP (CR: 87 vs. 87%; 2y-TTF: 80 vs. 83%; OS: 93 vs. 97%). Multivariate Cox-modeling adjusting for prognostic factors confirmed these results (disappearance of difference between CHOP and CHOP efficacy after R).

Conclusions: Differences between different CHOP-like regimens disappear when these regimens are combined with Rituximab for young good-prognosis patients with aggressive lymphoma.

RITUXIMAB (R) ADDED TO CHOP IMPROVES OUTCOME IN BCL-6 NEGATIVE BUT NOT IN BCL-6 POSITIVE DLBCL PATIENTS 0-40 YEARS

S. Horsing1, E. Wellert, S. Horning1, M. Krajewski2, D. Varjak05, T. Habermann1, R. Fisher1, P. Kurnt1, W. Macon1, M. Channahb1, R. Felger1, E. Hes1, L. Medeiros1, J. Weick1, J. Reed1, R. Gascogne2, Member, Eastern Cooperative Oncology Group, Boston, MA, USA; Research, Burnham Institute, La Jolla, CA, USA

An expert panel evaluated bcl-6 and bcl-2 protein expression by immunohistochemistry in 22 paraffin-embedded specimens from ECOG and SWOG cases enrolled on E4494, a randomized comparison of R-CHOP and CHOP, with or without maintenance R (MR) in DLBCL patients 2-60 years. Within the bcl-6 negative and positive subgroups there were no significant differences in clinical prognostic factors according to induction therapy. Three year failure-free survival (FFS) and overall survival (OS) were significantly higher for bcl-6 positive cases relative to bcl-6 negative cases, treated with CHOP (FFS: 54% vs. 49%; P = 0.001; OS: 76% vs. 17%, P = 0.005), but not R-CHOP (FFS: 41% vs. 66%; P = 0.21; OS: 58% vs. 78%, P = 0.19) in an analysis in which MR cases were not included. No differences were detected in FFS and OS for bcl-2 positive versus negative cases. When analyzed according to whether or not R was administered at any time, two year FFS was superior for bcl-6 positive cases relative to bcl-6 negative cases only among those who had not received R either as induction and/or maintenance therapy (64% vs. 13%, P < 0.0001). In a multivariate analysis of FFS, bcl-2, and treatment, CHOP vs. R-CHOP (weighted analysis) was the major determinant of FOS and OS, (HR = 0.1, P = 0.0004; HR = 0.1, P = 0.0005, respectively) for bcl-6 negative cases whereas treatment arm was not predictive in bcl-6 positive cases. FFS was the single significant predictor of outcome among the bcl-6 positive cases (FFS: HR = 3.6, P = 0.004; OS: HR = 7.9, P = 0.002). These findings suggest that R added to CHOP, whether as part of induction or maintenance, improves FFS and OS in bcl-6 negative cases but not bcl-6 positive cases.

B LYMPHOCYTE RECOVERY IN E1496: CVP +/- MAINTENANCE RITUXIMAB

S. Horning1, E. Wellert, H. Hochstein1, S. Frankel1, R. Gascogne et al.
1Thrombosis Committee, Eastern Cooperative Oncology Group, Boston, MA, USA; 2Lymphoma, Cancer and Leukemia Group B, Chicago, IL, USA

Background: Maintenance rituximab (MR) given at 375 mg/m2 weekly x 4 at 4 weeks after CVP (cyclophosphamide, vincristine, prednisone) and repeated at 6 month (M) intervals through 2 years resulted in significantly longer progression free survival (PFS) compared to observation (OBS) in stable and responding, indolent lymphoma pts (P < 0.0003; ASCO 2004).

Methods: Peripheral blood lymphocytes (Ly) and subsets were measured at specified time points. % and absolute CD20+ Ly counts were recorded at gestational age 21 (normal ≥131cells/mm3). B-cell recovery at or before each time point was computed.

Results: Median CD20+ Ly counts were normal at baseline but reduced after CVP in both groups. In the OBS group, CD20+ Ly recovered in 30%, 46% and 48% at 6, 12 and 18 months after CVP. Maintenance randomization in OBS pt compared to 1%, 1% and 1% in the MR group.

Conclusion: MR in the E1496 trial resulted in the absence of measured CD20+ Ly throughout the study period. Although rituximab-binding interferes with detection of CD20+ Ly, the reduction in total Ly is
consistent with a marked reduction/ absence of B-Ly. In either case, these data show a continued rituximab effect throughout the study period with the frequency of MR in E1496.

Absolute Lymphocyte Counts:

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<th>CD8+</th>
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THE INTERNATIONAL PROGNOSTIC INDEX (IPI) PRIOR TO TRANSPLANT IS AN IMPORTANT RISK FACTOR IN PATIENTS RECEIVING ALLOGENEIC STEM CELL TRANSPLANTATION FOR TREATMENT OF RELAPSED AGGRESSIVE LYMPHOMA

B. Glass 1, G. Wulff 2, J. Hasenkamp 3, W. Jung 4, L. Trimper 5, N. Schmitz 2
1 Abteil. Hämatolog und Onkologie, UKE Göttingen, Göttingen, Germany; 2 Hämatologie, AK St. Georg Hamburg, Hamburg; Germany

High dose therapy (HDT) followed by autologous stem cell support is of limited success in patients with primary progressive lymphoma, early relapse or relapse after primary HDT, respectively. We used intermediate intensity conditioning followed by allogeneic transplantation to address this problem. From July 2001 to June 2004 thirty two consecutive patients received Fludarabine 125 mg/m², Busulfan 8 to 12 mg/kg and cyclophosphamide 120 mg/kg prior to allogeneic peripheral blood progenitor cell transplantation. Mycophenolat mofetil plus cyclosporin A or Tacrolimus were used as GVHD prophylaxis. Thirteen pts had diffuse large cell NHL, 5 pts blastic mantle cell lymphoma, 5 pts Hodgkin's disease, 7 pts NK cell or T-cell lymphoma, 1 pt acute lymphoblastic leukemia and three pts a rapidly progressing follicular lymphoma. The median number of prior treatment regimens was 4. 19 pts received high-dose therapy and autologous SCT prior to alloSCT. Allo-PBPC were obtained from HLA-identical siblings in 12 pts, from matched unrelated donors in 20 pts. Engraftment of leukocytes was rapid (median 10 days, range 6–13) and all patients achieved complete (>95%) donor type chimerism after alloSCT. After one and two years, estimated overall survival is 59% and 53%, respectively. Treatment related mortality was substantial with 37% after one and two years, respectively. Relapse rate is 28% after one year. The number of prior therapies, prior HDT or status of disease (chemo-resistant versus chemo-sensitive disease) did not influence survival or TRM significantly. The age-adjusted IPI score prior to allogeneic SCT had a major impact on survival. Patients with IPI low and low-intermediate prior to allo-SCT had a survival of 72% one and two years after allo-SCT. Patients with high-intermediate and high IPI had a survival of 47% and 35% (P<0.05), after one and two years, respectively. Intermediate intensity conditioning followed by allogeneic SCT is an excellent treatment option in patients with high-risk relapse of malignant lymphoma as long as lymphoma burden can be controlled by salvage therapy prior to transplant. Patients with age-adjusted IPI high immediately prior to transplant have a worse prognosis but allo-SCT may still offer a chance of cure to some of them.

FRONT-LINE DOUBLE HIGH DOSE CHEMOTHERAPY (HDCT) WITH DICEP-BEAM AND AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCt) FOR POOR PROGNOSIS AGGRESSIVE NON-HODGKIN'S LYMPHOMA (NHL)

D. Stewart, K. Valentine, A. Balgh, D. Morris, C. Brown, A. Jones, J.A. Russell
Dept. of Oncology and Medicine, University of Calgary and Tom Baker Cancer Centre, Canada, Calgary

Introduction: One cycle of HDCT used as induction or as late consolidation therapy has not clearly been shown to improve survival of patients (pts) with poor prognosis aggressive NHL. We conducted an IRB approved, phase II study evaluating two cycles of induction HDCT for these pts.

Methods: Eligible pts (age 18–65 years, 2–3 AAPl risk factors, no serious comorbid disease) received CHOP x 1 cycle, then DICEP + G-CSF x 1 cycle (dose-intensive with autologous transplantation. 5.25 g/m², etoposide 1.05 g/m², cisplatin 105 mg/m²) for tumor cytoreduction and stem cell mobilization, and finally BEAM/ASCT (BCNU 300 mg/m², etoposide 800 mg/m², Ara-C 1600 mg/m², melphalan 140 mg/m²).

Results: From June 1998 to August 2004, 55 pts aged 20–63 years (median 44) were accrued, of whom 51 had diffuse large B-cell NHL. Poor prognostic factors included stage 4 (n = 45), >1 extranodal site (n = 18), elevated LDH (n = 47), ECOG 2–4 (n = 43), bolt >10 cm (n = 34), marrow involvement (n = 14). No pt experienced grade 3 or 4 regimen-related toxicity from DICEP or BEAM. Following DICEP + G-CSF, a median of 21 × 10⁹ CD34+ cells/kg (range 0–54.9) were collected. 51 pts received BEAM and 23 pts received involved field radiation to prior bulk. With a median follow-up of 38 months, 3 year event-free (EFS) and overall survival (OS) rates for all 55 pts are 77% and 79%, respectively.

Conclusion: CHOP-DICEP-BEAM is feasible and gave encouraging EFS and OS for pts with poor prognosis aggressive NHL.

FRONTLINE HIGH-DOSE THERAPY (HDT) FOR ADULTS WITH DISSEMINATED AGGRESSIVE LYMPHOMA (NHL): ANALYSIS OF 327 PATIENTS INCLUDED IN 3 PROSPECTIVE TRIALS (GOELAMS 071, 072, 074) OVER 12 YEARS

N. Milhied, E. Deconinck, P. Colombat, F. Goelams
Hematology, CHU, Nantes, France

We demonstrated in a randomised prospective trial (GOELAMS 072) that front line HDT including an autologous stem cell transplantation improved significantly the EFS and OS as compared to standard CHOP regimen in adults with aggressive NHL and a high-intermediate or high aa-IPI (NEJM 2004). In order to further precise the benefit and risks as well as the prognostic factors with that type of treatment we decided to analyse the patients who entered the high-dose arm of successive prospective GOELAMS' trials designed for patients 15 to 60 y.o. with non previously treated aggressive NHL (excluding mantle cell, Burkitt, Lymphoblastic and transformation of known low grade) A.A. stage II with abdominal bulk, III and IV, HIV neg and having given an informed consent (GOELAMS 071 BJH 2000; GOELAMS 072; GOELAMS 074 Blood 2004- ASH). Over a 12 years period 327 pts entered these trials. The median age was 44 yo, 60% male, 91% stage III/IV, 65% LDH-N, 33% PS2, 30% aa-IPI interm-low, 50% aa-IPI interm-high, 20% aa-IPI high. Histology was Diffuse large cell in 237, anaplastic in 29 and peripheral T cell in 16. Overall 75% of the pts received the planned treatment with autologous transplantation. The median FU for surviving patients is 57 m (2 to 148m). The KM 5 and 10y survival is 63% and 55% respectively. Overall 14 pts died a median of 13 m after inclusion (1–130m). The main cause of death was lymphoma relapse or progression (86 pts/75% of the deaths), 12 pts died from TRM: 4 from second cancer (3 solid, 1 MDS). In UV analysis prognostic factors for OS were: PS = 4, LDH=4xN, Peripheral T cell LNH. The median, KM 5y and 10y EFS are 77m, 51% and 49% respectively. In UV analysis prognostic factors for OS were LDH=4xN and Peripheral T cell LNH.
OUTCOMES OF SALVAGE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR RELAPSED OR REFRACTORY PRIMARY MEDIASTINAL LARGE B CELL LYMPHOMA ARE NOT INFERIOR TO BULKY DIFFUSE LARGE B CELL LYMPHOMA

J. Kuruvilla1, T. Nagy1, M. Pintiliie2, A. Keating1, M. Crump1
1University of Toronto, Autologous Blood and Marrow Transplant Program, Princess Margaret Hospital, Toronto, Canada; 2Clinical Study Coordination and Biostatistics, Princess Margaret Hospital, Toronto, Canada

INTRODUCTION: Gene expression studies have identified a distinct Primary Mediastinal Large Cell Lymphoma (PMLCL) profile when compared to Diffuse Large B Cell Lymphoma (DLBCL). While the results of primary therapy for PMLCL are generally superior to other subtypes of DLBCL, the outcome of salvage chemotherapy and autologous stem cell transplantation (ASCT) have not been well characterized. We evaluated the overall response rate (ORR) of this group of patients (pts) to second-line chemotherapy, progression-free survival (PFS) and overall survival (OS) in comparison to a group of pts with bulky (>5 cm) DLBCL.

METHODS: From an ASCT referral database, we identified 31 pts with PMLCL (between Jan 99-Dec 04) who were treated with salvage chemotherapy with intent to proceed to ASCT. All pts had received prior anthracycline-based chemotherapy. Pts typically received 2 cycles of platinum-based salvage chemotherapy to assess chemosensitivity, responding pts proceeded to PBSIC mobilization and subsequent ASCT (after high dose VP16 and melphalan).

RESULTS: At the time of salvage chemotherapy, PMLCL pts were a younger median age (34y, range 21-59 vs 53y in DLBCL, range 15-74) while the proportions of pts in a complete stage at salvage (45% PMLCL, 52% DLBCL pts, primary refractory (35% PMLCL, 58% DLBCL) and relapsed pts (45% PMLCL, 42% DLBCL) were similar. The ORR to first line salvage chemotherapy was similar (26% PMLCL vs 32% DLBCL, P = 0.55). The number of pts able to proceed to ASCT after salvage chemotherapy was similar (23% PMLCL vs 32% DLBCL, P = 0.15). At one year post initiation of salvage chemotherapy, the OS of the entire group was 56% (58% DLBCL vs 53% PMLCL, P = 0.61). At one year post-ASCT, the OS of the entire group was 71% (67% PMLCL vs 72% DLBCL, P = 0.71) and the PFS of the entire group was 53% (57% PMLCL vs 49% DLBCL, P = 0.79).

CONCLUSIONS: In a retrospective cohort comparison, relapsed or refractory PMLCL had a similar ORR, PFS and OS to salvage chemotherapy and subsequent ASCT when compared to pts with bulky DLBCL. This suggests that tumour bulk is an important factor and may be responsible for the poor outcomes seen in PMLCL that requires salvage chemotherapy. Gene expression studies may identify a unique profile in relapsed or refractory PMLCL cases and provide prognostic information to guide therapy.

ZEVALIN® (90Y) DOSES >5 MCI/KG MAY BE COMBINED WITH HIGH-DOSE BEAM AND AUTOLOGOUS TRANSPLANT (ASCT)

E. Winter1, D. Inwards2, S. Spies2, G. Wiseman3, D. Patton1, W. Erwin1, A. Rademaker1, S. Williams1, M. Tullman1, I. Micalef1, J. Mehta1, S. Singhal2, M. Zimmer1, A. Molina2, C. White1, L. Gordon1
1Hematology/Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; 2Hematology, Mayo Clinic College of Medicine, Rochester, MN, USA; 3Director, Biogen Idec Inc, Cambridge, MA, USA

33 patients with relapsed or refractory CD20+ NHL have been treated on an ongoing phase I trial of dose-escalated 90Y Zevalin followed by high-dose BEAM and ASCT in which the 90Y Zevalin dose is patient-specific and designed to deliver a tumor-defined radiation dose to critical organs (100-300 cGy). On D-22, rituximab (R) is infused followed by high-dose BEAM on D-5. Imaging is performed immediately at 4, 24, 72, and 144 hours; doximetry is performed on D-15. On D-14, R is followed immediately by 90Y Zevalin at the cohort-prescribed radiation dose to critical organs (100-300 cGy). On D-22, R is infused followed by high-dose BEAM. On D-1, patients receive high-dose BEAM. On D-10, G-CSF is begun. Median age was 55 range (25-72). NHL subtypes included 5 mantle cell, 16 DLBCL, 5 indolent, 7 transformed. Most had received 3-5 regimens, including R. The most common grade III/IV toxicities were infection, fever, stomatitis, nausea, vomiting, diarrhea, hemorrhage, and edema, similar to that seen with BEAM/ASCT. Engraftment occurred at a median of 10 days for ANC ≥500/ml and 21 days for platelets ≥20,000/ml. Median survival has not been reached (median follow-up 14 months); 3-year overall and progression-free survival are 63% and 43%, respectively. Patient-specific doses calculated to deliver a cohort-defined absorbed radiation dose to critical organs were highly variable (300 Gy: 0.45, 0.54, 0.81 mC/kg), suggesting that dosing based on weight and not dosimetry is likely to result in a wide range of absorbed dose to critical organs. 12 patients have safely received doses ≥0.5 mC/kg. Accrual continues at the 1500-cGy dose level.

YITTRIUM 90 (90Y) IBITUMOMAB TIUXETAN (ZEVALIN®) IN THE TREATMENT OF NON-HODGKIN'S LYMPHOMA (NHL); INCORPORATION INTO AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) REGIMENS

A. Nademanee1, A. Krishnan2, H. Fung3, A. Rabbitsch4, S. Forman1, A. Molina1
1Department Hematology/Bone Marrow Transplant, City of Hope National Medical Center, Duarte, CA, USA; 2Chao Comprehensive Cancer Center, University of California Irvine, Orange, CA, USA; 3Global Medical Affairs, Biogen Idec, Inc., San Diego, CA, USA

Background: Autologous and allogeneic SCT are effective therapies in select patients (pts) with NHL, but relapse is common. An analysis of 266 pts who underwent autologous SCT (ASCT) showed a reduced probability of relapse with a fractional total body irradiation (FTBI) -based regimen vs a chemotherapy-based regimen (P = 0.04) [Nademanee 2000]. Clinical trials are testing the efficacy of 90Y ibritumomab tiuxetan (ITX) when added to preenerative regimens for relapsed or refractory NHL.

Methods/Results: 2 studies at the City of Hope evaluated the safety and efficacy of high-dose or standard-dose 90Y IT combined with high-dose chemotherapy as preparative regimens for ASCT. Escalated 90Y IT with high-dose VP-16 and cyclophosphamide (CY) was used in pts with poor-risk or relapsed B-cell NHL (n = 31) [Nademanee, 2004 updated]. Median age was 51. The median dose of 90Y IT was 72 mCi (range 37-105). All but 1 patient engrafted. Remission was achieved in all pts with active disease at transplant; 5 pts relapsed. At a median follow-up of 22 mos, 2 yr OS and PFS were 92% and 78%, respectively. 1 pt died from alcohol-induced liver failure and another died of after-graft failure. A second study employed standard-dose 90Y IT (0.4 mCi/kg) + high-dose BEAM as a conditioning regimen for ASCT in older patients (median age = 60) with poor-risk NHL (n = 24)[Fung, 2003 updated]. Median WBC and platelet engraftment was at 11 and 13 days, respectively. At a median follow-up of 13 mos, OS and PFS were 94% and 74%. The relapse rate was 21%. Preparative regimens in these trials were generally well tolerated and transplant-related toxicity was similar to that observed with either high-dose VP-16 and CY or BEAM alone. Treatment-related toxicities were primarily hematologic.

Conclusions: High-dose 90Y IT plus high-dose VP-16 and CY is an effective preparative regimen for pts with refractory NHL, without increasing transplant-related toxicity or delaying engraftment. Moreover, standard 90Y IT with high-dose BEAM is well tolerated and effective in older pts undergoing ASCT for poor-risk NHL. These preliminary data suggest that the addition of 90Y IT to ASCT regimens produces increased anti-tumor activity without added toxicity.

SEQUENTIAL HIGH-DOSE CHEMOTHERAPY (SHDC) WITH AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) VS STANDARD CHOP REGIMEN FOR PTS WITH UNTREATED AGGRESSIVE NRL.. RESULT OF THE MISTRAL TRIAL FROM THE SWISS GROUP FOR CLINICAL CANCER RESEARCH (SACK)

Introduction: SHDC with ASCt has been shown to prolong the event-free survival in pts with diffuse large cell lymphoma (NEJM, 1997, 337). Methods: To confirm this result in a multicenter study, we randomized patients (pts) (600 pts) with aggressive NHL (diffuse, primary mediastinal and anaplastic large B-cell NHL) to receive either 8 cycles of CHOP (q21d) or SHDC (Phase I: standard CHOP; II: cyclophosphamide (7 g/m²); III: MTX (5 g/m²) and vincristine (2 mg); IV: etoposide (3 g/m²); V: mitoxantrone (60 mg/m²); melphalan (180 mg/m²)). Stem cells were collected after phase II or IV and reinfused after phase V. Radiotherapy was given to pts with bulky disease. The study was closed by the SAKK Scientific Committee after interim analysis. 35 centers from 5 countries recruited between 1 and 13 pts each. The primary endpoint was overall survival (OS).

Results: 136 pts (126 eligible, 131 treated) were randomized to CHOP (60) or SHDC (71) from 4/97 to 11/2003 (med. age: 48 yrs; 62% male; stage III+ IV: 73%; IPI 1/2/3: 21%/57%/26%; histology: 73% DLBCL, 16% mediastinal, 10% anaplastic NHL). 62% pts received the complete SHDC vs. 75% CHOP. Reasons for failure to receive ACt: 15 pts SD/PD or early death, 3 toxic death, 4 severe toxicity, 3 ineligible after reviewed histology, 2 unknown. Cross-over was allowed in pts not responding to R and rituximab (FCR) as a conditioning regimen for non-myeloblastic (NMA) allogeneic stem cell transplantation in patients (pts) with relapsed, chemosensitive NHL (Blood 989:3595, 2001). A more intense regimen however is needed for an early disease control in pts with refractory disease or in kinetic failure. We used the BEAM/R regimen for that purpose. Tacrolimus and Methotrexate were used for GVHD prophylaxis.

Methods: Seventy-two consecutive pts were treated. Sixty-one received FCR (median age 52; 24 with follicular, 24 with large cell and 12 with mantle cell NHL) and 11 had BEAM/R (median age 33, 10 had large cell and 1 follicular). Median # prior chemotherapies was 3. Sixty-two had a matched sibling donor, 7 had a matched unrelated, and 3 had a mismatched related donor.

Results: Outcome was as follows:

<table>
<thead>
<tr>
<th>Histology</th>
<th>Follicular (n = 25)</th>
<th>Large cell (n = 34)</th>
<th>Mantle Cell (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (3.5 yrs)</td>
<td>90%</td>
<td>64%</td>
<td>73%</td>
</tr>
<tr>
<td>DFS (3.5 yrs)</td>
<td>86%</td>
<td>65%</td>
<td>66%</td>
</tr>
</tbody>
</table>

Pts who received BEAM/R had more myelosuppression than those with FCR (% pts requiring platelets was 100% vs. 34%, respectively, P <0.001), had more acute 2–4 GVHD (45% vs. 16%, P = 0.02), and more chronic GVHD (91% vs. 47%, P = 0.001). One-year mortality for the FCR and BEAM/R groups was 27% and 25%. Pts with large cell within the 2 groups had, however, a comparable OS and DFS. Sixteen of 17 pts who failed a prior autologous transplantation (auto SCT) were alive, free of disease at a median follow-up of 36 mos (range 6–47 mos.). Fourteen patients with follicular lymphoma were tested for bel-2 by FCR. All were FCR (+) pre-transplant and they then converted to FCR (–) on sequential testings, up to 4 yrs post-transplant.

Conclusions: These data demonstrate that long-term remissions after NMA and reduced-intensity regimens can be achieved not only in indolent but also in pts with aggressive histologies. Prior auto SCT should not preclude pts from receiving this treatment.

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**ACUTE CARDIAC TOXICITY OF HIGH-DOSE CHEMOTHERAPY IN NON-HODGKIN'S LYMPHOMA PATIENTS UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANTATION**

K. Kutikovina, M. Husso-Saastamoinen, P. Sipola, O. Vuotienaho, N. Nousiainen, E. Janustain, J. Hartikainen

1Department of Medicine, Kuopio University Hospital, Kuopio, Finland; 2Department of Radiology, Kuopio University, Finland; 3Oulu University, Oulu University, Finland

**Introduction:** Non-Hodgkin's lymphoma (NHL) is among the leading indications for high-dose treatment (HDT). Even though cardiotoxicity is the most threatening non-hematological side-effect of high-dose cyclophosphamide (CY), very little is known about the real cardiac effects of CY in short time period.

**Patients and methods:** We prospectively evaluated the acute cardiac effects of high-dose CY in 17 adult NHL patients receiving high-dose CY 1500 mg/m² from d-6 to d-3 as a part of BEAC conditioning. Magnetic resonance imaging (MRI) and plasma natriuretic peptides (NT-porBNP, NT-porANP) measurements were performed prior to HDT (d-7) and after completing HDT (d-2) (d=0 day of stem cell infusion).

**Results:** During the CY infusion left atrial and left ventricular end-diastolic areas decreased from 20.6 ± 1.7 cm² to 24.3 ± 1.5 cm² (P = 0.002) and from 21.6 ± 1.6 cm² to 24.5 ± 1.6 cm² (P = 0.027) and right ventricular end-diastolic area from 19.8 ± 1.1 cm² to 24.1 ± 1.5 cm² (P = 0.001).

At the same time plasma levels of NT-porBNP increased from 134.9 ± 52.3 pmol/l to 547.1 ± 168.4 pmol/l (P = 0.003) and NT-porANP from 481.1 ± 105.5 pmol/l to 1056.6 ± 193.1 pmol/l (P = 0.001), respectively. However, no significant change in left ventricle ejection fraction (LVEF) was observed.

**Conclusions:** Our novel findings show that the acute cardiotoxicity of high-dose CY resulting in diastolic dysfunction can be detected with circulating natriuretic peptides but not with LVEF.

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**PACLITAXEL PLUS TOPOTEcAN PLUS RITUXImAB (TTR): AN EFFECTIVE SALVAGE PROGRAM FOR THE TREATMENT OF PATIENTS WITH RELAPSED/REFRACTORY AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMA (NHL)**


Lymphoma/Myeloma, M. D. Anderson Cancer Center, Houston, TX, USA

**Background:** To evaluate the efficacy and safety of the novel non-anthracyclin non-podophyllotoxin based TTR regimen in patients with relapsed and refractory aggressive B-cell NHL.

**Methods:** 72 eligible patients with diffuse large B-cell lymphoma, follicular center cell grade III, or transformed lymphoma were enrolled. Patients were allowed to receive a maximum of 2 prior treatment regimens, including platinum-based therapy. All patients received intravenous infusions of 375 mg/m² rituximab on day one, 200 mg/m² paclitaxel on day 2, Topotecan 1 mg/m² daily on days 2 through 6. On day 7 patients received daily filgrastim support until neutrophil recovery. Courses were repeated every 3 weeks. Responding patients were offered stem cell transplantation (SCT) after a minimum of 2 courses or continued to receive a maximum of 6 courses. 71 patients are evaluable for treatment response and toxicity, of whom 32 (45%) patients had primary refractory disease, and 20 patients (28%) received a prior platinum-containing regimen. Forty-one (57%) patients had an elevated pretreatment serum LDH level.

**Results:** Fifty of 71 (70%) patients responded (95% CI, 58%-81%). Including 42% achieving complete remissions (CR). The CR rate was higher in patients with relapsed disease than primary refractory disease (25% vs 56% respectively = 0.009). Furthermore, TTR induced a 45% response rate in the 20 patients who previously received platinum-containing regimens. With a median follow up of 26 months, the median duration of response was 21 months and 80% of responding patients who received SCT consolidation are alive at 3 years. Patients received
a total of 269 courses of therapy. Treatment was reasonably well tolerated and most non-hematologic toxicities were of grade 1 and 2. Grade 4 neutropenia was observed during 31% of the cycles, grade 4 neutropenic fever was observed in 7% of the patients Platelet count of less than 10,000/ml was observed during 5% of the cycles.

Conclusion: TTR is an effective new salvage therapy for patients with relapsed or refractory aggressive B cell NHL who failed prior CHOP-like or platinum-containing regimens.

AGGRESSIVE NON-HODGKIN'S LYMPHOMA IN THE ELDERLY: A VALIDATED PROGNOSTIC EVALUATION PERFORMED BY THE GRUPPO ITALIANO PER LO STUDIO DELLE LINFOMI (GISL)
P. Maggi1, I. Marcheselli2, M. Specchia1, S. Luminardi1, G. Pareschini1, A. Montanini1, V. Fregoni1, M. Federico1, F. Merli1
1:Ematologia, Ospedale S.G. Moscati, Taranto, Italy; 2:Oncologia ed Ematologia, Universita' di Modena e Reggio Emilia, Modena, Italy; 3:Medicina, Ospedale Civile, Sarno (MO), Italy; 4:Ematologia, Fondazione Maugeri, Pavia, Italy; 5:Ematologia, A.O. Arcispedale S.M. Nuova, Reggio Emilia, Italy

Introduction: Although age represents, per se, an adverse prognostic factor few data exist investigating the outcome of large series of elderly patients with aggressive NHL (aNHL).

Methods and objectives: We performed a retrospective multicenter analysis on patients older than 65 years, with aNHL, enrolled into clinical trials by the GISL from January 1988 until June 2003. The aim of the study was to evaluate prognostically some clinical parameters.

Results: Two-hundred and eighty nine patients were selected from the GISL databases and are the subject of the present analysis. The median age was 69 years (range 65–86) and 50% of the patients were male; 64% had stage III–IV disease, 16% bulky presentation, 9% P.S. 2–4, 28% fever, 38% elevated LDH, 56% albumin <4 g/dl, 15% Hb <10 g/dl, 34% ESR >50 mm. Patients were treated with PROMEC: Cytar BOM (60%), mini-CEOP (15%), P-VEBEC (14%) and different schemes (11%). A CR was achieved in 61% of the cases; the 4-yr OS was 45%. At univariate analysis the poorer OS (p<0.05) correlated with male gender, P.S. (≥3), stage (III–IV), B symptoms, elevated LDH (>UNR), anaemia (Hb <10 g/dl), low albumin (<4 g/dl) and elevated ESR (>50 mm). Sex, P.S., Hb and LDH were independent prognostic factors by Cox’s proportional hazard model. Age, explored both as continuous and as nominal variable did not affect significantly the outcome. A scoring system was formulated with three risk groups; patients at low (score=0), intermediate (score=1) and high risk (score=2–3) with a 5 yrs OS of 68%, 45% and 24% respectively.

Conclusion: In elderly patients with aggressive NHL it is possible to identify groups with different survival.

ROLE OF ANEMIA IN SURVIVAL OF PATIENTS WITH ELDERLY AGGRESSIVE NON-HODGKIN’S LYMPHOMA AFTER CHEMOTHERAPY
Institute of Hematology and Medical Oncology "L. & A. Seragnoi", University of Bologna, Bologna, Italy

Introduction: Baseline anemia is a relevant prognostic factor in the overall population of non-Hodgkin's lymphoma (NHL) patients, and studies focusing on elderly NHL are awaited.

Methods: We conducted a pooled analysis of a cohort of comparable patients enrolled (1993–2001) in three multicenter clinical trials on use of a MACOP-B-like regimen (VNCOP-B) for front-line treatment of grade 4 aggressive NHL. Models for Cox's proportional hazards regression analysis of prognostic value of pre/post-treatment hemoglobin values in terms of 3-yr overall survival included age, sex, initial tumor staging and response to treatment.

Results: Of the 168 patients screened, 16 were excluded due to missing data or lack of 3-yr follow-up. In addition to achievement of complete/partial remission (adjusted relative risk [RR], 0.215; P = .0001) and advanced stage (II–IV vs I–II; adjusted RR, 1.55; P = .0023), post-treatment hemoglobin values were an independent predictor of survival (adjusted RR per 1-g/dl increment, 0.76; P = .0041). In the present analysis, pretreatment hemoglobin values were associated with only marginal risk reduction (adjusted RR per 1-g/dl increment, 0.985; P = .049).

Conclusions: Post-treatment hemoglobin values appear to provide a stronger independent predictor of 3-yr survival in elderly aggressive NHL, supporting the potential role of anemia correction in this group of patients.

LYMPHOMA IN VERY ELDERLY PATIENTS MORE THAN 80 YEARS OLD: A RETROSPECTIVE ANALYSIS
C. Theoharmogi, A. Grossoevren, R. Hout, A. Michallet, C. Trauile, F. Bousafi, D. Espinouze, G. Salles, B. Coiffier
Hematology department, Centre Hospitalier Lyon Sud, Pierre-Benite, France

Introduction: Lymphoma in patients more than 80 years old is not a rare disease and therapeutic decision is often difficult. We retrospectively analyzed 205 patients over 80 treated in our center for lymphoma between 1989 and July 2004 to realize a descriptive analysis and to identify prognostic factors specific to this population.

Patients: Median age was 83, and sex ratio M/F was 0.79. Histologically, 91% of the cases were B-cell lymphomas, with a high predominance of DLBCL (n=81) and MZL (n=55). At diagnosis, 37% of the patients (pts) presented a PS ≥2 and 62% a disseminated disease. LDH and adjusted β2 microglobulin levels were increased in 43% and 32% of the cases, respectively. Half of the patients presented as anemia. IPI as it was elevated (≥2) in 82% of the pts. Classification of the pts in function of their comorbidity (number and gravity, Charlson scale) showed that, among the 87% of the pts with comorbidities, index was low in 38% of the cases, intermediate in 34% and high in 15%. Fourteen percent of the pts did not receive any treatment or corticoids only; 36% were treated by surgery, radiotherapy or monochemotherapy (CT): 18% by polycht without antracyclin, and 32% with polycyt with antracyclin. Among this group, only 8 pts received a standard treatment (6 or 8 cycles of CHOP or R-CHOP).

Results: Twenty-six percent of the pts obtained a complete response. Median overall survival was 2.21 years, and 1.31 years for pts with DLBCL. Causes of death (n=146) were a progression of lymphoma in 57% of the cases, a toxicity of the treatment (febrile neutropenia) in 16%, and were not related to the lymphoma in 14%. Prognostic factors for OS were PS (P<0.0001), LDH level (P<0.0001), stage (P<0.02), IPI (P<0.0001), anemia (P<0.02), and β2 microglobulin (P=0.005). Comorbidities were not found to influence survival.

Conclusion: Lymphoma in pts over 80 has is similar presentation and prognostic factors when compared to younger pts. Death is due in our series to the disease, meaning that these pts need to be treated with more standard treatment.

DOSE INTENSITY OF CHOP ALONE OR WITH RITUXIMAB IN DISEASE LARGE B-CELL LYMPHOMA (DLBCL) IN PATIENTS >60 YEARS OF AGE: AN ANALYSIS OF THE INTERGROUP TRIAL (CALGB 7983, ECOG-SWOG 4494)
V. Morrison1, E. Weller2, T. Habermann3, S. Li4, R. Gascoyne4, S. Horning5, R. Fisher2, B. Peterson5
1Hem/Onc, CALGB, Minneapolis, MN, USA; 2Biostatistics, ECOG, Boston, MA, USA; 3Hem, ECOG, Boston, MA, USA; 4Pathology, ECOG, Boston, MA, USA

The results of induction therapy with CHOP (cyclophosphamide [CTX], doxorubicin [ADR], vincristine, prednisone) alone or with rituximab (R-CHOP) in patients (pts) ≥60 yrs (age) of age with DLBCL have been reported (Blood 2003;102:6a; Blood 2004:104:40a). Pts were randomized at induction to receive 6–8 cycles of CHOP or R-CHOP. Responding pts (n=415) were then randomized to receive either no treatment or maintenance rituximab (MR). Per protocol, growth factors were not to be given with the 1st cycle of therapy, and thereafter ASCO guidelines were to be followed regarding their usage. Doses of myelosuppressive drugs (CTX/ADR) were dose-reduced by 50% in the subsequent cycle following an episode of febrile neutropenia. Doses of
these two agents were then increased to 75% full dose in the next cycle if no further complications occurred. The ability to deliver full dose CHOP therapy (defined as ≥85% average relative dose intensity [ARDI] in first 6 cycles) was evaluated in this older DLBCL, pt population, and compared by induction treatment. ARDI was also compared by baseline pt characteristics. Of the 632 pts enrolled on this trial, 527 (274 CHOP, 253 R-CHOP) were evaluable and had data on dose intensity. Median RDI for each agent approached 100% at each cycle; 78% and 74% of pts received full dose CTX and ADR, respectively, with no differences detected by induction therapy (R-CHOP vs CHOP: 78% vs 76%, P=0.50). Percent of pts with ARDI for CTX/ADR ≥85% was significantly lower for pts ≥75 yrs of age (70% vs 80%, P=0.03) and for stage I-II pts (73% vs 79%, P=0.05), and was marginally lower for pts with baseline hemoglobin ≥12 g/dl (73% vs 90%, P=0.09). In conclusion, these data demonstrate that ARDI of CHOP and R-CHOP, specifically of CTX/ADR, can be maintained in a majority of pts ≥60 yrs with DLBCL, and that the addition of R does not impact ARDI.

**Objectives:** To compare the efficacy of CHOP and PmIcCebO and the addition of prophylactic G-CSF in either regimen.

**Patients and Methods:** Recruitment included newly diagnosed patients aged ≥60 yrs with bulky stage IA, stages IB-IIV aggressive NHL. Eligible patients were randomized in a 2:1 factorial design to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) + G-CSF, CHOP, PmIcCebO (prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin, vincristine) + G-CSF or PmIcCebO. CHOP was given as a weekly alternating regimen for 5 weeks. Prolymphocytic leukaemia was administered if randomised to G-CSF from days 8–14 in the CHOP arm and days 6–12 in the PmIcCebO arm.

**Results:** Between October 1997 and September 2003, 784 patients (195 CHOP, 192 CHOP + G-CSF, 202 PmIcCebO, 195 PmIcCebO + G-CSF) from 92 centres in the UK were randomised. Patient characteristics were balanced between arms: median age 70 yrs, 8% male, age adjusted international prognostic index risk score of 0.2.3 was 16%, 30%, 37% and 17% respectively. Complete response rates were 61% for CHOP + G-CSF, 58% for CHOP, 51% for PmIcCebO + G-CSF and 51% for PmIcCebO. Overall response rates were 90% for CHOP + G-CSF, 89% for CHOP, 89% for PmIcCebO + G-CSF and 95% for PmIcCebO. At a median follow-up of 40 months, there was no statistical difference in progression free survival (PFS) among all the four arms (log rank P=0.22). There were no differences in DFS in the comparisons between CHOP and PmIcCebO, and no G-CSF (P=0.14).

**Conclusions:** Comparability of efficacy was achieved with CHOP and PmIcCebO. Prophylactic G-CSF did not influence the outcome. Toxicity was equivalent in all groups. PmIcCebO is therefore a safe and efficacious alternative for patients with aggressive non-Hodgkin’s lymphoma who cannot tolerate a doxorubicin-containing regimen.

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**IS IT POSSIBLE TO CURE ELDERLY PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA? A RELATIVE SURVIVAL ANALYSIS OF THE R-CHOP STUDY (GELA-LNH98) WITH LONG-TERM RESULTS**

M. Touzi1, M. Henry-Amar1, J. Bries1, C. Gieselbrecht1, F. Reyes1, P. Graulard1, P. Lederlin1, C. Sebban1, A. Bosly1, P. Morel1, H. Tilly1, R. Bouabdallah1, B. Coiffier2

**GELA, Hospital St Louis, Paris, France; 2GRECAN, CLCC Baclesse**

**Purpose:** In patients with diffuse large B-cell lymphoma (DLBCL), deaths during the first two years mostly reflect treatment failure or relapse. In the other hand, delayed deaths could be due to age-associated morbidity. We aimed to analyze the long-term outcome of patients included in the LNH98-5 study comparing CHOP to R-CHOP plus rituximab (R-CHOP) by focusing on the relative survival (RS). This new approach compares the overall survival (OS) in the study population with the survival in the general population.

**Patients and Methods:** LNH98-5 study included 399 DLBCL patients, aged 60 to 80 years. They received 8 cycles of CHOP every 3 weeks. In R-CHOP, rituximab was given at the dose of 375 mg/m². Follow up data was updated in 2004. RS were computed as the ratio between OS in the study population and the expected survival in the general population matched for age and gender (www.isee.fr).

**Results:** 4-yr OS was 53.9% and 4-yr RS was 60.8% (P=0.046). The benefit of R-CHOP in OS (P=0.007) was also confirmed in RS (P=0.007). 4-year OS and RS were 48.2% and 53.8% in the CHOP group (P=0.001), and 59.4% and 67.6% in the R-CHOP group (P=0.23), respectively. To estimate the probability of cure (i.e. when annual relative mortality rate equal 0) in survivors we computed the annual relative mortality rates during the third, the fourth and the fifth years. They were, in the CHOP group: 8.9%, 4.2% and 2.4%; in the R-CHOP group: 5.7%, 2.7% and 1.5%.

**Conclusion:** Combination of rituximab plus CHOP is now the standard for treating elderly patients. However, there remains an excess of mortality (1.5%) when compared with the general population.
THE MYOCAN PHASE II STUDY OF CYCLOPHOSPHAMIDE, ONCOVIN, MYOCET™ AND PREDNISONE + RITUXIMAB (R-COMP) IN ELDERLY PATIENTS WITH DIFFUSE LARGE B-CELL (DLBCL) NON-HODGKIN LYMPHOMA

M. Federico1, M. Caballero2, M. Dyer3, S. Luminari3, E. Thier1
1Department of Oncology and Hematology, University of Modena and Reggio Emilia, Modena, Italy; 2Dept. of Haematology, Hospital Clinico Universitario, Salamanca, Spain; 3Dept. of Haematology, University of Leicester, Leicester, UK; 4Dept. of Haematology and Oncology, Charité Campus Benjamin Franklin, Berlin, Germany

BACKGROUND: For more than 20 years, CHOP has been the gold standard treatment for patients with aggressive NHL. The addition of rituximab to this regimen has been shown to improve outcomes in elderly patients with advanced NHL (Coiffier et al. NEJM 2002: 346:235-42). However, CHOP is often poorly tolerated by elderly patients resulting in dose reductions and consequently lower response and cure rates compared to younger patients. The PK profile of Myocet™ (non-pegylated liposomal doxorubicin) results in less myelosuppression, GI toxicity and has a reduced risk of cardiotoxicity compared to standard formulations of doxorubicin.

METHODS: In this phase II, open label, 2-stage study, we replaced conventional doxorubicin with Myocet™ to evaluate response rate and safety of the R-COMP regimen. Previously untreated, elderly patients (260 yrs) with CD20+ newly diagnosed, advanced DLBCL, were treated every 3 weeks with: Myocet™ 50 mg/m², cyclophosphamide 750 mg/m², vincristine 1.4 mg/m² (max. 2 mg), rituximab 375 mg/m² (d3 cycle 1, d1 thereafter) and prednisone 100 mg/d from 1–5 for 8 cycles. Response was assessed after 3 and 8 cycles.

RESULTS: For the 30 patients enrolled in stage I of the study, the median age was 72 (range 61–82), 56% patients had stage III-IV disease, 60% had an intermediate or high risk (2+) IPI score and median LVEF was 59% (range 50–75). A total of 198 cycles of chemotherapy were given (median 8, range 1–8). Of the 198 cycles administered, 15 (8%) were delayed by haematological or hepatic toxicity for a median of 7 days (range 0 to 25). The relative dose intensity for the regimen was 87%. Toxicity was mainly haematological with grade 3 or 4 neutropenia in 29% of cycles and febrile neutropenia in 4%. There was no grade 3 or 4 vomiting and a low incidence of grade 1 or 2 vomiting (3%). At the last observation, the median LVEF was 55% (range 40–76), 3 patients were withdrawn due to reduced LVEF. Of 24 patients evaluable for final response, 15 (63%) had a complete response and an additional 7 (29%) achieved a partial response. A total of 58 patients have been enrolled now, in 33/38 patients assessable for response after 3 cycles 14 (38%) had a CR or nCR, 17 (46%) PR, 2(5%) PD.

CONCLUSIONS: These interim results suggest R-COMP is a well tolerated regimen with promising response rates in elderly patients with advanced DLBCL.

CISPLATINUM, IDARUBICIN, PREDNISONE (CIP) AFTER P-VABEC CHEMOTHERAPY IMPROVES SURVIVAL IN ELDERLY PATIENTS WITH DIFFUSE LARGE CELL LYMPHOMA: LONG TERM FOLLOW-UP

M. Martelli, F. Caracciolo, A. Perrotti, E. Iannitto, V. De Sanctis, A. Andriani, M. Giovannini, M. Montanaro, F. Natalino, E. Finolezzi, F. Mandelli, R. Fusi, M. Petri
Hematology Univ. La Sapienza, on behalf of an Italian Cooperative Study Group, Rome, Italy

BACKGROUND: P-VABEC regimen resulted a safe and active therapy for elderly patients (pts) with DLCL. However in spite of an high response rate, the overall and lymphoma free survival decrease for an high incidence of relapses.A phase II study demonstrated that CIP regimen was an active and safe regimen.

AIMS: To compare the activity and toxicity of CIP consolidation therapy after P-VABEC versus a standard P-VABEC regimen in a prospective multicenter randomized phase III study.

METHODS: From October 1995 to June 2000 we enrolled 214 previously untreated elderly pts with DLCL. The median age was 70 yrs (range 60–85). Patients were randomized at diagnosis to receive P-VABEC (arm A) or P-VABEC-CIP (arm B). The P-VABEC regimen was delivered on outpatient basis as previously described. The CIP regimen consisted of:

Cis-platinum (40 mg/m² day 1), Idarubicin (15 mg/m² day 8), and Predni-sone (40 mg/m² days 1–4/8–11) q. 21 days for a total of 3 courses. Now 202 pts are evaluable for response, 107 pts randomized for P-VABEC and 95 for P-VABEC-CIP. According to the age-adjusted IPI score 89 pts were considered as Low Risk (IPI 0–1) and 113 as High Risk (IPI 2–3).

RESULTS: At a median follow up of 52 months (range 1–99) the CR/CRu rate was 58% and 64% (P=ns), the 5-ys OS was 41% and 60% (P=0.011) and 5-ys PFS 39% and 53% (P=0.05) respectively in arm A and arm B. According to the IPI score in the High Risk the 5rys OS was 25% vs 52% (P=0.008) and 5-ys PFS was 25% vs 36% (P=ns) for Arm A and Arm B respectively with in the Low Risk no significant difference was found. Thirteen/202 (13%) toxic deaths related to chemotherapy occurred, all during P-VABEC induction therapy.

CONCLUSIONS: P-VABEC-CIP resulted a safe chemotherapy regimen and improves survival in this group of elderly pts with DLCL.