''focus on...'' session: primary mediastinal and other extranodal lymphoma

039 DIFFUSE LARGE B-CELL LYMPHOMA WITH RENAL INVOLVEMENT: OUTCOME AND RISK OF CENTRAL NERVOUS SYSTEM RELAPSE

D. Villa[1], J.M. Connors[1], S.H. Laurie[1], R.D. Gascoyne[1], K.J. Savage[1]
[1]*Division of Medical Oncology, British Columbia Cancer Agency, Vancouver, Canada*

Background: Renal involvement is uncommon in diffuse large B-cell lymphoma. In a recent study, our group found that renal involvement was an independent risk factor for central nervous system (CNS) relapse (Villa, ASCO 2007). We reviewed the clinical features, risk of CNS involvement, and survival for an expanded cohort of patients.

Methods: All patients with DLBCL and renal extranodal involvement diagnosed from January 1, 1982 to August 1, 2007 at the British Columbia Cancer Agency were retrospectively identified in the Lymphoid Cancer Database. Patients were included if they were >16 years old, had advanced stage (stage III /IV, or stage I /II with B symptoms or bulky (>10cm)) disease, were treated with curative intent and free of CNS involvement at diagnosis.

Results: There were 46(2%) patients with DLBCL with renal involvement at diagnosis identified with the following characteristics n(%): M:F 2.3:1; median age 59 y; 19(41) had bilateral renal involvement; 42 (91) had stage IV disease; 43(94) IPI 3,4 or 5; 7(15) had a GFR < 30 mL/min; 39(85) had an elevated LDH. With respect to therapy, 9(20) patients received CHOP plus rituximab (CHOPR), 27(59) received CHOP-like regimens and only 8(17) patients received intrathecal prophylaxis. In total, 15 patients (33%) have had a CNS relapse (leptomeninges 9; brain parenchyma 5; both 1). The median time to CNS relapse was 5.6 mos. There was no significant difference in presenting clinical features between those who had a CNS relapse and those who did not. The addition of rituximab did not reduce the risk of CNS relapse (6/19 32% CHOPR vs 9/27 33% CHOP-like, p=.90) or time to CNS relapse (p=.49). The 5y overall and progression-free survivals for the whole cohort were 29% and 28%, respectively, suggesting that salvage therapies are ineffective. Patients receiving CHOPR chemotherapy had an improved 5y progression free (43% vs 18%, p=.12) and overall (49% vs 19%, p=.04) survival.

Conclusion: There is an exceptionally high incidence of CNS relapse in patients with DLBCL and kidney involvement at diagnosis. The addition of rituximab appears to improve overall survival in this poor risk population, likely through improved control of systemic disease.

040 LONG-TERM FOLLOW-UP OF THE C5R PROTOCOL OF HIGH-DOSE CHEMOTHERAPY AND RADIOTHERAPY IN 100 NEWLY DIAGNOSED PRIMARY CNS LYMPHOMAS: A PROSPECTIVE MULTICENTRIC PHASE II STUDY OF THE GELA

H. Ghesquieres[1], C. Ferlay[2], C. Sebban[3], O. Casasnovas[4], O. Reman[5], A. Bosly[6], B. Coiffier[7], P. Biron[8], J. Blay[9]
[1]*Hematology, Centre Leon Berard, Lyon, France, On Behalf of Groupe d'Etudes des lymphomes de l'Adulte (GELA),* [2]*Statistique, Centre Leon Berard, Lyon, France,* [3]*Hematology, Centre Leon Berard, Lyon, France,* [4]*Hematology, University Hospital, Dijon, France,* [5]*Hematology, University Hospital, Caen, France,* [6]*Hematology, Hospital Mont Godine, Yvoir, Belgium,* [7]*Hematology, CHLS, Pierre Benite, France,* [8]*Hematology, Centre Leon Berard, Lyon, France,* [9]*Oncology, Centre Leon Berard, Lyon, France*

Introduction: This prospective multicentrique phase II study aimed to confirm the feasibility and results of the C5R protocol a high-dose (HD) methotrexate-based chemotherapy designed for immunocompetent patients with primary CNS lymphoma (PCNSL).

Patients and Methods: Between 1995 and 2002, 100 HIV-negative patients with newly diagnosed PCNSL received age-adapted doses of chemotherapy followed by 20 Gy whole-brain radiotherapy and 30 Gy boost to the tumour bed. Patients younger than 61 years (Group 1 n = 45) received the full C5R with HD methotrexate, adriamycin, vincristine, cyclophosphamide and cytarabine. Patients aged 61-70 years (Group 2 n = 37) received reduced doses of methotrexate, cyclophosphamide and adriamycin. Patients older than 70 years (Group 3 n = 18) received 4 courses of methotrexate, cyclophosphamide and etoposide.

Results: Median age was 63 years (range, 20-82) and 51% presented with poor performance status. Histology was diffuse large cell lymphoma in 78%. 9% and 24% patients died of toxicity in groups 1 and 2-3, respectively. Complete response at completion of treatment was achieved in 64%, 76% and 33% in groups 1, 2 and 3, respectively. With a median follow-up of 83 months, the 5-year progression-free survival probability was 31%, 28% and 11% (p = 0.02) and the 5-year overall survival probability 42%, 31% and 17% for groups 1, 2 and 3, respectively (p = 0.01). Leucoencephalopathy occurred in 32% patients.

Conclusion: Full C5R for younger patients was feasible in the multicentric setting, with high response rates and excellent survival after long-term follow-up. Results in older patients were disappointing that incline to reconsider the therapeutic strategy for these patients.

041 CHLAMYDIA INFECTION AND LYMPHOMA: MULTIPLE DETECTION METHODS HIGHLIGHT AN ASSOCIATION BEYOND LYMPHOMAS OF THE OCULAR ADNEXA

M. Ponzoni[1], A.J. Ferreri[1], M. Guidoboni[2], A.A. Lettini[2], M.G. Cangi[1], E. Pasini[2], L. Sacchi[3], L. Pecciarini[1], S. Grassi[1], E. Dal Cin[1], R. Stefano[1], S. Magnino[4], R. Dolcetti[2], C. Doglioni[1]
[1]*Unit of Lymphoid Malignancies, San Raffaele Scientific Institute, Milano, Italy,* [2]*Cancer Bioimmunotherapy Unit, Centro di Riferimento Oncologico, Aviano, Italy,* [3]*Animal Biology, University of Pavia, Pavia, Italy,* [4]*National Reference Laboratory for Animal Chlamydioses, IZSLER, Pavia, Italy*

Background: Chlamydophila psittaci (Cp) has been associated, with variable geographic distribution, to ocular adnexal lymphomas (OAL) through PCR-based strategies; data on the role of other Chlamydia detection tools, the identification of the cells containing Cp elementary bodies and the assessment of the prevalence of Cp in nodal and extranodal lymphomas are not available.

Methods: TETR-PCR, immunohistochemistry, immunofluorescence, electron microscopy, and laser-capture microdissection were evaluated in 35 OAL to define their value in Chlamydia detection and to identify the cellular carriers of Cp. The concordance between immunohistochemistry and TETR-PCR was assessed in 54 cases encompassing lymphomatous and non-neoplastic disorders. Fifty-eight nodal, 147 extranodal, extra-orbital lymphomas, respectively and 74 non-neoplastic controls underwent TETR-PCR to define the prevalence of Cp infection in these groups.

Results: Twenty-six (74%) OAL were associated with Cp infection: immunohistochemistry, immunofluorescence and laser-capture microdissection-assisted PCR showed that monocytes/macrophages were the carriers of Cp, whereas electron microscopy demonstrated intact Cp elementary bodies inside them. Immunohistochemistry and TETR-PCR showed a 70% (p= 0.001) concordance rate. Cp DNA was equally prevalent in extranodal and nodal lymphomas: among extranodal, non-OAL, it was significantly more common in diffuse large B-cell lymphomas of the skin and Waldeyer's ring.

Conclusion: We demonstrate for the first time, through a multiparametric approach, that monocytes/macrophages are the carriers of Cp. This microorganism is preferentially associated with lymphomas arising in organs considered primarily exposed to antigens. Further insights on the lymphomagenetic role of Cp and potential therapeutic implications are added.

042 STAT6 ACTIVITY IS REGULATED BY SOCS-1 AND MODULATES BCL-XL EXPRESSION IN PRIMARY MEDIASTINAL B-CELL LYMPHOMA

O. Ritz[1], C. Guiter[2], K. Dorsch[1], I. Dusanter-Fourt [3], S. Wegener[1], H. Jouault [2], P. Gaulard[2], F. Castellano[2], P. Möller[1], K. Leroy[2]
[1]*Pathology, University of Ulm, Ulm, Germany,* [2]*Pathology, INSERM U841; Université Paris 12, Cretel, France,* [3]*Hematology, INSERM U567; Institut Cochin, Paris, France*

Background: Primary mediastinal B-cell lymphoma (PMBL) is a distinct subtype of diffuse large B-cell lymphoma, which has been recently shown to exhibit activated Signal Transducer and Activator of Transcription (STAT) 6 and frequently mutated or deleted Suppressor Of Cytokine Signaling (*SOCS*)-1 genes.

Material and methods: PMBL derived cell lines MedB-1 and Karpas1106 were transfected with plasmid vectors encoding wild type SOCS-1 or shRNA / siRNA against STAT6 and compared to mock transfected cells. Expression of total and Phosphorylated (P) – STAT6 were analyzed by Western blot and cell cycle and cell viability were analyzed by flow cytometry. The regulation of *BCL-XL*expression by STAT6 was studied using chromatin immunoprecipitation and quantitative RT-PCR assays in transfected cells, and immunohistochemistry in primary PMBL tumor samples.

Results: Expression of wild type SOCS-1 strongly reduced the transcriptional activity of STAT6 and induced cell death in MedB-1 and Karpas1106. Downregulation of STAT6 with shRNA or siRNA was associated with a significant increase in the rate of cell death and a significant decrease in the proportion of cells in S-phase in MedB-1 cells. STAT6 was bound to the *BCL-XL*promoter in PMBL cell lines and STAT6 downregulation was associated with a parallel decrease of *BCL-XL* mRNA and protein levels in MedB-1 cells. Moreover, in PMBL tissue, nuclear P-STAT6 accumulation correlated with BCL-XL cytoplasmic expression in neoplastic cells.

Conclusions: Our results show that *SOCS-1*gene defects have pro-survival effects and strongly contribute to STAT6 activation in PMBL cell lines. STAT6, in turn, activates BCL-XL expression and regulates cell proliferation and survival in PMBL cells.

043 THE ADDITION OF RITUXIMAB TO DOSE-ADJUSTED (DA)-EPOCH OBVIATES THE NEED FOR RADIATION IN THE TREATMENT OF PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMBL): A PROSPECTIVE STUDY OF 58 PATIENTS

K. Dunleavy[1], S. Pittaluga[1], J. Janik[1], N. Grant[1], M. Shovlin[1], S. Steinberg[1], M. Raffeld[1], E.S. Jaffe[1], L.M. Staudt[1], W.H. Wilson[1]

[1]*Center for Cancer Research, National Cancer Institute, Bethesda, United States*

Background: PMBL is a distinct clinicopathological entity with a predilection for young females and a molecular signature overlapping with classical HL(cHL). As with cHL, the risk of local failure after anthracycline-based therapy has led to the routine use of mediastinal RT. RT has serious late toxicities in young patients and strategies that avoid its use are needed.

Methods: We prospectively evaluated DA-EPOCH+/-R without routine RT in 58 sequential patients with PMBL. 18 received DA-EPOCH alone; the next 40 DA-EPOCH+R. DA-EPOCH was given for 6-8 cycles as described (Blood 99: 2685, 2002).

Results: Most patients had adverse prognostic features. IHC profiling in 54 biopsies showed CD20+ in 100%, CD10+ 5%, BCL-6+ 81%, and MUM-1 + 48%. At a median potential follow-up of 10.9 and 3.3 years, PFS and OS were 67% and 78% for DA-EPOCH; 93% and 100% for DA-EPOCH-R. Adding R significantly improved PFS (p=0.019) and OS (p=0.017) by 2-tailed exact log-rank test. 2 patients had + biopsy at end of therapy: 1 underwent resection and 1 IFRT. In f/up, 2 patients relapsed with local disease: 1 received CT/RT; 1 RT alone.

Conclusions: DA-EPOCH-R is highly effective in PMBL with OS of 100%: 92% of patients did not require/receive RT. Accrual continues.

	DA-EPOCH	DA-EPOCH-R
Patients	18	40
F:M	10:8 (1.25)	23:17 (1.35)
Median age, Y (range)	34 (20-62)	32 (12-70)
Median mass cm (range)	8.4 (5.1-15.7)	10.5 (3-19.7)
Stage III/IV	50%	32%
LDH > N	78%	67%
ECOG PS > 1	11%	5%
Extranodal sites	50%	40%
Pl. Effusion	22%	35%

044 RITUXIMAB DOES NOT IMPROVE SURVIVAL OF PATIENTS TREATED WITH M/VACOP-B PLUS RADIOTHERAPY IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMLBCL): AN ITALIAN PHASE II STUDY OF INTERGRUPPO ITALIANO LINFOMI (IIL)

M. Martelli[1]

[1]*Hematology Department, University La Sapienza, Rome, Italy, On Behalf of Intergruppo Italiano Linfomi (IIL)*

Introduction: M/VACOP-B regimens in combination with involved-field radiotherapy (IFRT) seem to improve survival of PMLBCL. The superiority of R-CHOP over CHOP has been demonstrated in randomized trials. The addition of Rituximab to CHOP has also improved the survival of PMBLCL. Our study aimed to evaluate the effectiveness and safety of Rituximab added to M/VACOP-B regimens (R-M/VACOP-B) +/- IFRT in PMLBCL.

Patients and methods: Forty-five patients (pts) with PMLBCL have been treated in 6 Italian centers between February 2002 and July 2006. The median age was 38yrs (range 17-66); 24/21 (53%) were females; 32 pts had stage IIand 13 IIE-IV; 42 (95%) had a bulky disease; LDH was increased in 31(69%) and 24(55%) had a superior vena cava syndrome. All pts were treated with standard MACOP-B (35 pts) or VACOP-B (10pts) regimens plus 6 cycles of Rituximab (375mg/m^2) given at weeks 3,5,7,9,11,13. Thirty-two pts (71%) received mediastinal IFRT at a median dose of 30-36 Gy. The response was evaluated in all pts after 6-12 cycles of R-M/VACOP-B and after IFRT.

Results: The response rate after 6 cycles was CR/CRu=20 (45%), PR=24 (54%) and NR=1 (2%). Three/45 PR pts received an intensification with HDT-ASCT after 6 cycles due medical decision in spite of the planned protocol. At the end of 12 cycles, 26 pts witnessed a CR/CRu (62%), 15 a PR (36%) and 1 NR (2%). Eight/17 PR pts obtained a CR/CRu following IFRT for an overall CR/CRu rate of 34/42 (80%). Five patients (2 CR, 3 PR) relapsed within 19 months from end of therapy and died of progressive disease. After a median follow-up of 25months, the 2-year OS and PFS were 80% and 84%, respectively. In a our historical group of 92 pts with PMBCL treated with MACOP-B+IFRT without Rituximab the 5-yrs OS and PFS were 87% and 81% respectively.

Discussion: R-M/VACOP-B are active therapeutic regimens devoid of severe toxicity in PMBCL. Consolidation radiotherapy seems to improve the quality of response. Further studies are required to demonstrate if the addition of Rituximab to M/VACOP-B regimens may truly improve the response rate and survival of PMBCL.