Focus on... session: primary mediastinal BCL

146 BORTezoMIB (BTZ), iKk InHIBITor ML120B, AND cOMBINATION tHERAPY INduce aPOTOPSIS, inhibIT NF-kB ACTIVATION, AND DECREASE SPECIFIC PROTEINS IN PRIMARY MEDIASTINAL B-CELL LYMPHOMA (pMBL)

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Background: PMBL is a subtype of diffuse large B-cell lymphoma (DLBCL) with a lower EFS in children than other identically treated DLBCLs (Patte/Caire et al., Blood, 2007). Unlike germinal center B-cell like (GCB) DLBCL, PMLB shows NF-kB activation similar to classical Hodgkin lymphoma. Bortezomib (BTZ) inhibits the NF-kB pathway indirectly by blocking proteosomal degradation of IKB, while the novel small molecule IKK inhibitor ML120B specifically targets NF-kB pathway signaling. Therefore, we investigated apoptosis, NF-kB pathway inhibition, and differential protemic expression in a PMLB cell line treated with BTZ and ML120B.

Methods: PMBL (Karpas 1106) or GCB (SUDHL-6) cells were treated with ML120B (10 mg/mL) and/or BTZ (5 mg/mL) for 24 hours and assayed using the Annexin V-FITC Apoptosis Detection Kit I (BD Pharmingen), the TransAm NF-kB activation kit (Active Motif), and the Human Apoptosis Array Kit (for Caspase 3; R&D). Quantitative proteomic analysis was performed using iTRAQ tandem mass spectrometry and data were validated by western blots.

Results: BTZ induced apoptosis in PMBL (16.5±4.6% vs. untreated control, p<0.05) and GCB (58.8±5.8% vs. 0.01% cells), while ML120B induced apoptosis in the PMBL (14.4±0.95% p<0.05) but not GCB (4.4%±0.9%, p=NS) cells. NF-kB pathway proteins were activated in untreated PMBL cells, with p50/p65/p52 (Red(Re)/Red). ML120B caused inhibition of p50 (32% vs. untreated control, p<0.01), Red (31% ±0.05, p<0.01), and p65 (55% ±0.01) activation but not of RelB activation. BTZ inhibited p52 (-9%, p<0.01) and RelB (1%, p<0.05). ML120B + BTZ caused significant inhibition of all factors and led to the highest expression of caspase 3 (350±53 vs. 55±5 pg/mg protein, p<0.006). ML120B induced a significant (>2 fold) decrease in the levels of 28 proteins in PMLB cells by iTRAQ analysis including small nuclear ribonucleoprotein, HSP90 (heat shock protein 90), phosphofructokinase, citrate synthase, and DDX24 (ATP dependent RNA helicase 24). BTZ significantly decreased 36 proteins, and the combination of BTZ and ML120B decreased 28 proteins. Western blotting confirmed the decrease of 7/8 proteins in response to ML120B.

Conclusions: The IKK inhibitor ML120B increased apoptosis alone or in combination in PMBL but not GCB cells. These findings suggest that specific targeting of the NF-kB pathway may improve therapeutic responses in PMBL, and clinical trials should be considered in the future.

147 PEt/CT RESPONSE ANALYSIS IN PRIMARY mediASTINAL DIFFUSE LARGE B-CELL LYMPHOMA (PMBL): PRELIMINARY RESULTS OF THE IELSG-26 STUDY

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The need for radiotherapy in patients with PMBL responding to immunochemotherapy is an unresolved issue. The IELSG-26 study was designed to obtain prospective data in a single cohort regarding the treatment outcomes following anthracycline-containing immunochemotherapy, with or without mediastinal irradiation, according to the local practice of the participating institutions. The primary endpoint was the 18-F-FDG PET response rate following systemic therapy. Between 2007 and 2010 the study enrolled 125 patients with PMBL who received R-CHOP(-like) or R-MACOP-B(-like) regimens. 123 received consolidation radiotherapy. PET-CT scans were performed at baseline, at 3-4 weeks after the end of immunochemotherapy and 2 months after completion of radiotherapy, according to a standard protocol. CT-CT Complete Response (CR) was defined according to the criteria of the International Harmonization Project by a negative scan or one having minimal residual uptake (MRU) less than the mediastinal blood pool (MBP) activity in regions which were FDG-PET positive at baseline. Central review has been performed of the CT-CT images at the end of chemotherapy in the first 61 patients. The scans showed metabolic CR in 30 pts (43%); in 5 cases (8%) the CT-CT scan was completely negative but in 25 (41%) there were small residual masses with 18-F-FDG uptake less than MBP. Out of 31 (51%) positive CT-CT scans the residual uptake was > MBP but < liver uptake in 17 (28%) cases, slightly > liver uptake in 10 (16%) and >> liver in 4 (7%). The agreement between central review and local reporting was only 70% (43/61). The rate of positive scans on central review was 51%, compared to 39% on site, mainly due to underestimation of the MRU > MBP < Liver. The proportion of patients with positive CT-CT scans at end of immunochemotherapy is higher than has been reported in diffuse large B-cell lymphoma. This may be attributable partly to relatively short interval between the end of chemotherapy and imaging, and partly to low level residual uptake at the site of previous bulky mediastinal disease. Analysis of the CT-CT response and its correlation to clinical outcomes in the whole cohort will be presented.

148 THE IMPACT OF R-VACOP-B AND THE PROGNOSTIC SIGNIFICANCE OF INTERIM FDG-PET/CT ON THE OUTCOME OF PATIENTS WITH PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA- A RETROSPECTIVE ANALYSIS OF A SINGLE CENTER COHORT

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Background: Primary mediastinal large B-cell lymphoma (PMBCL) is a relatively rare subtype of DLBCL. The choice of a rituximab-based regimen and the prognostic significance of interim FDG-PET/CT in this entity are still debatable issues.

Methods: We evaluated the clinical features and outcomes of 95 consecutive patients with PMBCL who were treated in Sheba Medical Center between 1985 and 2009.

Results: 43 patients received rituximab-based chemotherapy: R-VACOP-B (n=30) or R-CHOP21 (n=13), whereas 52 patients were treated with VACOP-B (n=46) or CHOP21 (n=5) in the pre-rituximab era. Radiotherapy was not given following initial chemotherapy. During the 85-month median follow-up, the overall (OS) and progression-free survival (PFS) at 5 yrs for all patients were 92% and 65%, respectively. Patients who received rituximab as part of treatment had 5-yr PFS of 79% and OS 97% compared with 58% (P=0.06) and 88% (P=0.2), respectively, without rituximab. Notably, 5-yr PFS in patients treated with R-VACOP-B, R-CHOP21, VACOP-B or CHOP21 were 83%, 69%, 62% and 20%, respectively (P=0.039). However, direct survival comparison showed that the difference between PFS rates in patients receiving R-VACOP-B compared to R-CHOP21 was not statistically significant (P=0.3). None of the standard clinical risk factors predicted for PFS in patients receiving R-chemotherapy, while pleural effusion was the only predictor of reduced PFS (P=0.003) in the pre-rituximab era. Mid-interim FDG-PET/CT scans were performed in 30/43 patients who received R-VACOP-B (n=19) or R-CHOP21 (n=11). The negative predictive values of mid-PET activity were high (100% in R-VACOP-B and 86% in R-CHOP21), while the positive predictive values (PPV) were relatively low (30% and 75%, respectively). Despite the low PPV, overall, the 5-yr PFS for mid-PET negative patients (n=16) was significantly higher (94%) than for mid-PET positive patients (n=14) (57%, P=0.015).

Conclusion: This single center-based retrospective analysis demonstrates that the superiority of VACOP-B over CHOP21 for treatment of PMBCL disappears once rituximab is included. The results further suggest that mid-PET activity has a prognostic impact on the outcome of patients with PMBCL. The role of rituximab-based regimens other than R-CHOP and the prognostic significance of interim PET in these patients warrant further consideration in larger randomized studies.
Background: Primary Mediastinal B cell lymphoma is a distinct subtype of diffuse large B-cell lymphoma that is more common in younger female age. Combined regimen of chemotherapy (CT) with involved field radiotherapy (IFRT) is considered the mainstay of treatment. In the pre-Rituximab era third generation regimens as MACOP-B has improved survival in PMBL patients (pts) over CHOP, but the current combination of Rituximab with CHOP regimen equalize this difference. The real need of consolidation mediastinal IFRT is still debated for the risk of secondary cancer and cardiac disease. We report the long term results on a large series of PMBL treated at our institute.

Method: 107 pts with PMBL were treated between June 1991 and September 2006; 80 pts had stage II and 27 stage III-IV, 75% had elevated LDH, bulky disease was in 95 pts including 58 (55%) with clinical evidence of superior vena cava obstruction. Median age was 34 yrs (15-61), 71% were females. The IPI score was 0-1 in 60 pts and 2-3 in 47. Ninety-two pts were treated with standard MACOP-B regimen and 15 received a R-chemotherapy since March 2004. Overall 94% received IFRT at dose of 30-36 Gy. The response was evaluated at the end of CT and of IFRT.

Results: At the end of the program, the CR/CRu was obtained in 76 pts (71%), PR in 23(21%), NR 1(1%), 7 pts were not evaluable: 6 pts received an early intensification for progressive disease and 1 died for toxicity by CT. At the end of the program: 14 of PR pts obtained a PET negative CR after a R-chemotherapy regimen. These results indicate MGZL is distinct from PMBL and based on clinical and IH characteristics appears more similar to NSHL. Comparative gene expression profiling (GEP) of 15 cases each of untreated MGZL, PMBL and NSHL is underway.

Characteristics | PMBL (n=40) | MGZL (n=16) | p2
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Male sex | 38% | 75% | 0.017
Median Age (range) | 32 (19-52) | 30 (14-51) |
Median Mass (cms) | 11 (5-18) | 11.8 (6-20) |
Stage III/IV | 30% | 12% |
LDH > N | 77% | 62% |
Extranodal sites | 57% | 25% | 0.039
Pleural effusion | 52% | 12% | 0.007
Immunohistochemistry CD20+ | 100% | 100% |
BCL6+ | 86% | 100% |
CD30+ | 71% | 100% | 0.14
CD15+ | 0 | 60% | 0.0009
Outcome (47mos) | |
EFS | 95% | 45% | 0.0002
OS | 100% | 75% | 0.0036

Conclusions: This is the largest reported series of PMBL treated at single center. MACOP-B +/- Rituximab plus IFRT is highly effective and devoid of a severe long term toxicity. Future randomized trials should evaluate the real need of a mediastinal IFRT in pts who obtained a PET negative CR after a R-chemotherapy regimen.