session 4 – diffuse large B-cell lymphoma

050 GENE EXPRESSION SUBTYPES OF DIFFUSE LARGE B CELL LYMPHOMA ARISE BY DISTINCT GENETIC PATHWAYS

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Introduction and methods: Gene expression profiling has been used to define three molecular subtypes of diffuse large B-cell lymphoma (DLBCL): germinal center B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL and primary mediastinal B-cell lymphoma (PMBL). To investigate whether these DLBCL subtypes arise by distinct pathogenetic mechanisms, we analyzed 203 DLBCL biopsy samples by high resolution, genome-wide copy number (aCGH) coupled with gene expression profiling. We defined minimal common regions (MCRs) that were recurrently altered in copy number and identified those that dysregulated the expression of their constituent genes. Statistical differences in MCR frequency between DLBCL subtypes were corrected for multiple hypothesis testing using a false discovery rate (FDR) calculation.

Results: Of 258 MCRs that occurred in more than 5% of any DLBCL subtype, 31 were utilized differentially by the DLBCL subtypes (p<0.005, FDR rate <0.05). Amplification of the oncogene involved in the pathogenesis of ABC DLBCL.

Conclusion: aCGH revealed novel copy number abnormalities in transcription factor. Knockdown of oncoproteins affected by the chromosome 18 aberrations. An amplicon on chromosome 18q is recurrently altered in copy number and identified those that dysregulated the expression of their constituent genes. Statistical differences in MCR frequency between DLBCL subtypes were corrected for multiple hypothesis testing using a false discovery rate (FDR) calculation.

052 LIMITED-STAGE DLBCL PATIENTS WITH A NEGATIVE PET SCAN FOLLOWING THREE CYCLES OF R-CHOP HAVE AN EXCELLENT OUTCOME FOLLOWING ABBREVIATED IMMUNO-CHEMOTHERAPY ALONE

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Background: DLBCL treated with CHOP but not R-CHOP on E4494. Now, with a median followup of 6.85 years, we update the analysis of this prospective correlative study of prognostic markers including p21 and p53 in addition to bcl-2 and bcl-6.

Material/Methods: EOCOG or SWOG patients enrolled in the phase III US Intergroup trial comparing CHOP to R-CHOP with or without maintenance R (MR) were eligible. Since 2005, we have recommended that all patients with limited-stage DLBCL (stage I/II, no B-symptoms, mass < 10 cm) treated in British Columbia (BC) undergo a PET scan following three cycles of R-CHOP; PET-negative patients are then offered one additional cycle of R-CHOP, while PET-positive patients receive IFRT. To date, 65 patients have been treated according to this algorithm with the following clinical characteristics: median age 67 y (range 31-88); 58% male; 58% stage I, 42% stage II; 5% PS 5-1; 2% elevated LDH; 57% at least 1 extranodal site. Stage-modified IPI risk factors remained powerful predictors of outcome in the R-CHOP era, providing clues to underlying survival pathways and to putative targets for drug development.

Results: At 2 years, estimated progression-free survival (PFS) and overall survival (OS) were prolonged for those treated with R-CHOP alone compared to CHOP alone (5-year PFS: 71% vs 6%, p=0.001; 5-year OS: 79% vs 5%, p<0.0001). In contrast, no differences in PFS and OS were detected between treatment arms for Bcl-6+ cases (n=154; p=0.85 and 0.26). There was no association between Bcl-6 and p21 immunostaining (p=0.72). The prognostic profile differed according to treatment arm. For patients treated with R-CHOP, the independent prognostic indicators were p21+ (FFS: RR 0.3, p=0.002; OS: RR 0.4, p=0.003), Bcl-2+ (FFS: RR 2.3, p=0.01; OS: RR 3.6, p=0.002), and the IPI (HR: high FFs: RR 4.5, p=0.002; OS: RR 5.6, p=0.001). Only Bcl-6 immunoreactivity (FFS RR 0.2, p=0.001; OS RR 0.2; p<0.0001) predicted outcome in CHOP treated patients. Among patients treated with R-CHOP, Bcl-2+/p21+ cases had a better FFS and OS compared to all other patients (p=0.02; p=0.02), whereas Bcl-2-/p21 cases did less well (p=0.02; p=0.06). P53 immunoreactivity did not predict for outcome in univariable analysis (p=0.22).

Conclusion: The addition of R to CHOP improves outcomes in identifiable biologic subsets of DLBCL and thereby alters its prognostic profile. P21, Bcl-2 and the IPI remain powerful predictors of outcome in the R-CHOP era, providing clues to underlying survival pathways and to putative targets for drug development.

053 IMPROVED OUTCOME OF ELDERLY PATIENTS WITH POOR-PROGNOSIS DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) AFTER DOSE-ENSEMBLE RITUXIMAIB: RESULTS OF THE DENSE-R-CHOP 14 TRIAL OF THE GERMAN HIGH-GRADE NON-HODGKIN LYMPHOMA STUDY GROUP (DSHNHL)

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Background: While to 6 of 8 cycles of CHOP in combination with rituximab (R) are widely accepted as standard regimen for aggressive lymphomas, the optimal dose and number of R application have not yet been determined. In a previous pharmacokinetic study we had shown that the concomitant application of CHOP and R does not achieve a plateau of R trough levels until cycle 5 (Reiser, Blood 108, 778a, 2006).

References:

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054 SEQUENTIAL RCHOP AND YTTRIUM-90 IBRUTUMOMAB TRUDEXAN (RIT) IS A HIGHLY EFFECTIVE REGIMEN FOR HIGH RISK ELDERLY PATIENTS WITH UNTREATED DLBCL

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Introduction: Elderly patients (pts) 60 years with aaIPI HI or H risk disease have a 5 yr survival (OS) rates of 37%, and 21%, respectively. Rituximab’s addition to CHOP has improved outcomes, but >50% of high risk pts still relapse. We hypothesized consolidation of RCHOP with 90Y ibritumomab tiuxetan radioimmunotherapy (RIT) would improve outcomes by eradicating minimal residual disease.

Methods: Untreated ASCT- ineligible pts 60 yrs old with aIPI HI or H risk DLBCL are eligible. Induction: standard RCHOP q 21 days by 6 sessions of RCHOP pts with poor prognosis (IPI>3) disease (81% vs. 68%) and in a better 1-year EFS-rate (74% vs. 65%) of these pts.

Conclusion: RCHOP-R-CHOP-14 resulted in a higher CR-rate of pts with poor-prognosis (IPI>3) disease (81% vs. 68%) and in a better 1-year EFS-rate (74% vs. 65%) of these pts.

054bis FIRST RESULTS OF AN INTERNATIONAL STUDY TO ESTABLISH A NEW CLINICO-BIOLOGICAL PROGNOSTIC INDEX FOR DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

The Lunenburg Lymphoma Biomarker Consortium (LLBC)

Background: Due to lack of sufficient validation, prognostic biomarkers in DLBCL have not gained a broad acceptance and thus far the International Prognostic Index (IPI) remains the only standard for practical clinical use. Clinical factors of the IPI however represent surrogates for the underlying biology. The LLBC aims to move risk stratification beyond the IPI by performing systematic biomarkers validation with the following steps.

Methods: Based on the availability of pathology material suitable for tissue microarrays (TMA) and a minimum 3-year follow-up, cases from 13 prospective studies for DLBCL pts were selected from 7 LLBC collaborative study groups. Disease, treatment and outcome characteristics were collected in a single LLBC database from studies incorporating CHOP (or CHOP-like) chemotherapy regimen as the standard arm (n=1117) or more recently comparing CHOP (n=620) vs Rituximab (R)-CHOP (n=620). TMAs were generated, centrally stained and circulated for triple independent scoring of 8 immunohistochemical markers using criteria previously defined and validated (de Jong et al, JCO 2007). Optimal cut-points for overall survival (OS) prediction were first assessed based on the earlier CHOP studies and their prognostic significance was evaluated on randomized R-CHOP studies.

Results: Analyzed cases covered the complete distribution of risk and age groups both for R- and non-R- treated pts. With a 5-year median follow-up, median OS was 7.6 years, and the IPI was found to be predictive both for CHOP and R-CHOP pts (p<0.0001). Biomarker data were available for 1424 cases with all 8 markers evaluable in 756 cases. Cut-points for OS prediction in CHOP pts were defined as 575 vs <75% for Bcl-2 (Hazard Ratio=1.79; P<0.004) and MUM1 (HR=1.13; P=0.029), no staining vs staining for Bcl-6 (HR=0.57; P=0.003) and CD5 (HR=1.53; P=0.0072) and negative vs positive for HLA-DR (HR=0.59; P=0.0008), respectively. No optimal cut-point could be determined for Ki67 and CD10 as single markers predictive of outcome. Bcl-2, Bcl-6 and MUM1, but not CD5 or HLA-DR cut-points were validated in the independent series of randomized CHOP pts. In R-CHOP treated pts, only Bcl-2 (HR=1.53; P=0.032) and CD5 (HR=1.85; P=0.0072) were found to predict patient outcome.

Conclusion: Using a validated approach on a large series of pts, this study 1) establishes optimal non-arbitrary cut-points for candidate prognostic biomarkers in DLBCL, 2) provides a rational basis for their combination and the design of biologically relevant algorithms and 3) enables one to assess their influence in the rituximab era. Data detailing the design of a new biological IPI (BPI) for DLBCL patients will be discussed.