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Lymphoma Trials in low grade and high grade lymphomas in Germany – Results of prospective randomized trials support the use of chemo-immunotherapy and define the role of front-up dose escalation strategies

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Cooperative trial groups for low grade lymphoma (Chair: W. Hiddemann, M.D.) and high grade lymphoma (Chair: M. Pfreundschuh, M.D.) in Germany cooperate within a federally funded competence network lymphoma (KML: www.lymphome.de) that serves as a platform for the structural organization of quality control measures like reference pathology, monitoring and for the dissemination of scientific knowledge to practicing physicians and patients. The two large trial groups accrue more than 1000 pts annually into large phase III trials. In addition, several phase II trials are active. Supported by these trial groups, scientific studies accompanying these clinical trials are organized in a network called “Molecular mechanisms of malignant lymphoma” (Chair: L. Trümper & H. Stein) that focuses on genetic analyses of lymphoma samples from pts treated within clinical trials. Gene expression as well as cytogenetic and molecular genetic analyses are the aim of this network.

In low grade lymphoma, separate trial strategies for follicular grade I & II and mantle cell lymphoma are active. In successive trials, CHOP was established as the standard treatment basis for advanced follicular and mantle cell lymphoma. In early stages, radiation as low dose TBI and IF radiation are prospectively compared. In a large multicenter trial conducted between 1996 and 2000, 307 pts younger than 60 years were treated with CHOP for 6 or 8 cycles followed by consolidation with either BEAM and stem cell rescue or interferon maintenance therapy. For pts undergoing transplant, after a median

observation of 4.4 years, PFS was 64.7 % as compared to 33.3% for the interferon treated pts. In a second trial, untreated FCL pts were randomized in a large multicenter trial to either CHOP or R-CHOP as front-up treatment. Of 428 fully evaluable pts, 205 were treated with CHOP and 223 with R-CHOP. R-CHOP reduced the estimated risk of treatment failure by 2.5 fold compared to CHOP alone. The overall response rate was increased from 90% to 96%. Overall survival was increased even considering the short observation time (Hiddemann et al., 2004). Therefore, CHOP + rituximab is considered standard therapy for advanced FCL in Germany. Whether consolidation by high dose chemotherapy or by rituximab maintenance is advantageous is currently being tested in another randomized trial. The trials confirm that with systemic chemoimmunotherapy, a very high rate of remissions can be achieved and also, that maintenance strategies are of additional value in FCL.

In aggressive lymphoma, trials were conducted between 1994 and 2000 to show the value of dose density and dose intensification by interval shortening (CHOP-14) and addition of etoposide to CHOP (Pfreundschuh, Trümper et al., Blood 2004). These trials showed that with dose-dense CHOP, remission rates as well as survival in elderly patients with aggressive lymphoma can be significantly increased. Therefore, CHOP-14 is the standard treatment for elderly aggressive lymphoma pts in Germany. In a second trial that was terminated by the advisory board in December 2003, young low- and intermediate risk pts

with aggressive B-NHL were treated with either CHOP-like chemotherapy or CHOP-like therapy + rituximab. The first formal interim analysis was performed on 326 evaluable patients with confirmed CD20 positive DLBCL (median age 44 years; 76% stage I/II, 24% stage III/IV disease, 31% elevated LDH, 50% bulky disease). Patients randomized to R-CHEMO had a higher complete remission rate (84.7% vs. 66.0%; $p=0.0002$) and a lower rate of progressive disease (6.3% vs. 17.7%; $p=0.0039$). Patients in the R-CHEMO arm had a significantly longer TTF ($p=0.000038$; log rank test) and overall survival ($p=0.0057$; log rank test) compared to the CHEMO arm. At a median observation time of 15 months, TTF rates were 84% for R-CHEMO and 62% for CHEMO respectively (Pfreundschuh, Trümper et al., ASCO 2004). In high-risk patients below 60 years of age, sequential high dose therapy with maximally escalated CHOP-etoposide (Mega-CHOEP) and stem cell rescue has been tested in a large non-randomized phase II trial (Glass, Schmitz et al, 2004). The addition of rituximab to the sequential therapy was tested in a recent phase II trial. From June 01 to February 03, 89 pts were enrolled in the study, 80 were eligible. As of August 03, 37 pts were evaluable after median observation time of 17 months. 20/37 pts completed all cycles of chemo- and immunotherapy, additional 7 patients received all 4 cycles of chemotherapy and 4 out of 6 cycles rituximab. 30/37 pts (81.1 %, 95% CI 68,5-93,7%) achieved CR or CRu 3 months after last cycle of therapy. This approach is currently tested against standard CHOP-etoposide in 14-day intervals in a prospective phase III trial.

Recent results and treatment strategies of the German lymphoma groups will be presented at the meeting.

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