StiL Beteiligung ASH 2009

405 Bendamustine Plus Rituximab Is Superior in Respect of Progression Free Survival and CR Rate When Compared to CHOP Plus Rituximab as First-Line Treatment of Patients with Advanced Follicular, Indolent, and Mantle Cell Lymphomas: Final Results of a Randomized Phase III Study of the StiL (Study Group Indolent Lymphomas, Germany)

Oral and Poster Abstracts
Oral Session: Lymphoma: Chemotherapy, excluding Pre-Clinical Models - Non-Hodgkin Lymphoma: Therapy
Monday, December 7, 2009: 11:00 AM
208-210 (Ernest N. Morial Convention Center)

Mathias J Rummel, MD, PhD[1*], *Norbert Niederle*[2*], *Georg Maschmeyer*[3], *Andre Banat, MD, MBA*[4*], *Ulrich von Gruenhagen, MD*[5*], *Christoph Losem*[6*], *Gerhard Heil*[7*], *Manfred Welslau*[8*], *Christina Balser*[9*], *Ulrich Kaiser*[10*], *Harald Ballo*[11*], *Eckhart Weidmann*[12*], *Heinz A Duerk*[13*], *Dorothea Kofahl-Krause*[14*], *Fritz Roller*[15*], *Juergen Barth*[16*], *Dieter Hoelzer, MD, PhD*[17], *Axel Hinke*[18*] *and Wolfram Brugger*[19]

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Introduction: Promising results have been observed in two phase-II studies evaluating the combination of Bendamustine plus Rituximab (B-R) in patients with relapsed/refractory indolent or mantle cell lymphomas (Rummel et al., JCO 2005; Robinson et al., JCO 2008). In order to further investigate the role of the combination B-R we initiated a multicenter randomized phase-III study in October 2003 to compare efficacy and safety of B-R versus CHOP plus Rituximab (CHOP-R) as first-line therapy for patients with follicular (FL), indolent and mantle cell lymphomas (MCL).

Patients and Methods: 549 patients (pts) in need of treatment for their disease were randomized to receive Rituximab 375 mg/m^2 (day 1) plus either Bendamustine 90 mg/m^2 (days 1+2) every 28 days or the standard CHOP regimen every 21 days for a maximum of 6 cycles. The primary endpoint was progression-free survival (PFS). Patients characteristics, including age, stage, LDH, IPI, FLIPI, bone marrow infiltration and extranodal involvement did not statistically significant differ between both arms. The median patient age was 64 years (range 31-83) (64 yrs for B-R and 63 yrs for CHOP-R). Most patients were in stage IV (76,9% in BR and 77,5 in CHOP-R) and stage III (19,2% in B-R and 18,6% in CHOP-R). Histologies were distributed equally between B-R and CHOP-R: follicular 55% and 56%, mantle cell 18% and 19%, and other indolent lymphomas 27% and 24%, respectively. Prophylactic use of antibiotics or growth factors were not generally recommended in this protocol.

Results: Of the 549 pts 36 pts were not evaluable: 10 did not receive any study medication, 9 due to withdrawal of consent, 13 due to incorrect diagnosis (4 x DLBCL, 3 x CLL, 2 x MM, 1 x HD, 3 x solid tumors), and 4 for other reasons. 513 randomized pts are evaluable for the final analysis (B-R: n=260; CHOP-R: n=253). Out of these 9 pts were not evaluable for response evaluation: 4 pts (3 x CHOP-R, 1 x B-R) due to early death in neutropenic sepsis, 3 pts due to a subsequent change of therapy after severe toxicity in 1st cycle of CHOP-R, 1 B-R pt due to progress of disease, and 1 B-R due to early death. All patients were counted for evaluation of PFS, overall survival (OS), event-free survival (EFS; an event was defined by a response less than a partial response, disease progression, relapse, or death from any cause), and for time to next treatment (TTNT).

A median number of 6 cycles was given in both treatment arms each. 82% of B-R pts and 86% of CHOP-R pts received 6 cycles. At the time of analysis in August 2009, the median observation time was 32 months. Overall response rate for pts treated with B-R was similar to the CHOP-R group (93,8% vs 93,5%, respectively). The CR rate was significantly higher with 40,1% for B-R compared to 30,8% for CHOP-R (p=0.0323). The median

PFS, EFS and TTNT were significantly longer after B-R compared to after CHOP-R: PFS 54,8 months for B-R versus (vs) 34,8 months for CHOP-R (p=0.0002), Hazard Ratio (HR) 0.5765 (95% confidence interval (CI) 0.4292 to 0.7683); EFS 54 months for B-R vs 31 months for CHOP-R (p=0.0002, HR 0.6014 (95% CI 0.4515 to 0.7845); and TTNT median not yet reached in the B-R group vs 40,7 months in the CHOP-R group (p=0.0002; HR 0.5416, 95% CI 0.3897 to 0.7491). OS did not differ between both groups at this point of time. Thus far, 67 deaths have been observed (B-R: 34; CHOP-R: 33).

CHOP-R treatment was more frequently associated with serious adverse events (SAE) (n=49 in B-R vs n=74 in CHOP-R). Significant differences in hematologic toxicities were observed for neutropenia grade 3+4 (BR 10,7% vs CHOP-R 46,5%; p<0.0001) and for leukocytopenia grade 3+4 (BR 12,1% vs CHOP-R 38,2%; p<0.0001). G-CSF was more often used in CHOP-R treated pts (20,0% of all cycles) than it was used in the B-R group (4,0%) (p<0.0001). The B-R regimen was better tolerated by the pts as evidenced by a lower rate of alopecia (15% (only grade 1) in B-R vs 62% CHOP-R), a lower number of infectious complications (95 in BR vs 121 in CHOP-R, p=0.0403), a lower incidence of peripheral neuropathy (B-R n=18; CHOP-R n=73; p<0.0001), and fewer episodes of stomatitis (B-R n=16; CHOP-R n=47; p<0.0001). Only drug-associated erythematous skin reaction (urticaria, rash) was more often seen with B-R (n=42) than with CHOP-R (n=23) (p=0.0122).

Conclusions: In this final analysis the combination of Bendamustine plus Rituximab improves PFS and CR rates while showing a better tolerability profile. These promising results suggest that B-R does have the potential to become a new standard first-line treatment option for patients with FL, MCL, and indolent lymphomas.

Disclosures: Rummel: *Roche Pharma AG:* Honoraria, Research Funding; *Mundipharma:* Honoraria, Research Funding; *Amgen:* Honoraria. **Maschmeyer:** *OrthoBiotech:* .

http://ash.confex.com/ash/2009/webprogram/Paper20178.html

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441 Quantitative Real-Time PCR of Peripheral Blood t(14;18) Positive Cells Predicts Treatment Response and Long-Term Outcome in Patients with Follicular Lymphoma

Oral and Poster Abstracts
Oral Session: Non-Hodgkin's Lymphoma - Biology, excluding Therapy: Genetic Factors in Lymphoma
Monday, December 7, 2009: 11:00 AM
E-1 (Ernest N. Morial Convention Center)

Fabian Zohren[1*], *Ingmar Bruns, MD, PhD*[2], *Juergen Barth*[3*], *Sabrina Pechtel*[4*], *Roland Fenk*[5*], *Thomas Schroeder*[6*], *Akos G. Czibere, MD*[7], *Georg Maschmeyer*[8], *Dorothea Kofahl-Krause*[9*], *Gerhard Heil*[10*], *Norbert Niederle*[11*], *Christoph Losem*[12*], *Manfred Welslau*[13*], *Ulrich Germing*[14*], *Ralf Kronenwett*[4*], *Rainer Haas*[15*], *Mathias J Rummel, MD, PhD*[16*] *and Guido Kobbe, MD*[17*]

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Introduction:

By means of standard chemotherapy advanced stage follicular lymphoma (FL) is an incurable disease. Clinical courses are characterized by a continuous tendency to relapse caused by residual neoplastic cells. Quantitative

polymerase chain reaction (qPCR) to detect lymphoma cell that carry the t(14;18) translocation is a suitable method to measure minimal residual disease (MRD) in patients with FL. Despite several reports dealing with MRD qPCR in FL, its role in the clinical management of patients is still not clearly defined. Therefore, we carried out a multicenter study, to assess the prognostic value of sequential quantitative MRD detection in first-line treatment of FL using an *improved version* of a LightCycler based qPCR specific for the major breakpoint region (MBR) positive IgH/bcl2 translocation, provided by Roche Diagnostics® (Penzberg Germany).

Patients and Methods:

We analysed 718 blood (PB) samples of 179 patients with newly diagnosed FL treated within the multicenter randomized trial NHL1, conducted by the German StiL group (Study group indolent Lymphomas), comparing 6 cycles of R–CHOP *versus* R–Bendamustin (R-B). Samples were taken at diagnosis, after 6 cycles of either R–CHOP or R–B immuno-chemotherapy and every three months during follow-up. All samples were analyzed in the department of Hematology at Heinrich-Heine University in Duesseldorf.

Results:

At diagnosis, 112 out of 179 patients (62.6%) were positive for IgH/bcl2 within the MBR in the peripheral blood. Significantly higher amounts of bcl2/IgH positive cells were found in patients with bone marrow infiltration (p=0.012) and depending on the number of lymphatic nodes (LN) with disease involvement (>3 LN p=0.003; >5 LN p=0.0009; >7 LN p=0.022). Overall, a remarkable inter-individual variation of bcl2/IgH positive cells in the PB at diagnosis, reflected by ratios from 0.000281 to 81, was found. The estimated event free survival (EFS) at 2 years of patients who presented at diagnosis low to normal amounts of bcl2/IgH positive cells in the PB (ratio < 2, n=83) was 82% (SE 0.045), which was significantly better than the 47% (SE 0.11) observed in patients showing the highest amount of bcl2/IgH positive cells (ratio >2, n=24) in the PB (p=0.003). By univariate and multivariate analysis, we found that the amount of bcl2/IgH positive cells in the PB at diagnosis (p=0.001) as well as the achievement of a negative MRD status after therapy (p=0.0001) were significant predictors for relapse free survival. Monitoring of MRD levels before and after therapy revealed that 6 cycles of immuno-chemotherapy significantly reduced the amount of bcl2/IgH positive cells in the PB compared with pre-treatment MRD levels (p=0.0001; median bcl2/IgH/tPA ratio: before treatment 0.0734, range: 0.000281–81, after treatment negative, range: negative–0.17). After treatment, 86% of the patients (n=82) achieved a molecular remission in the PB defined as qPCR negative, whereas 14% (13 patients) remained PCR positive. Not reaching a molecular remission in the PB at the end of therapy had a significant negative influence on PFS. After a median follow-up of two years, patients who remained MRD positive in the first measurement after therapy had a significant lower PFS than MRD negative patients (p=0.0001; 9 months vs. not reached). There was no significant difference in the degree of tumor cell depletion in the PB induced by the two different regimens. So far, 539 follow-up samples from 3 up to 39 months after therapy were analyzed. Patients with a consistent negative MRD status throughout follow-up showed a trend towards longer PFS. After 38 months follow-up, MRD positive patients had a PFS of 54% compared to 78% in the group of MRD negative patients (p=0.066).

Conclusion:

QPCR for the t(14;18) performed at diagnosis and during follow-up on PB samples predicts treatment response and long-term clinical outcome of patients with FL.

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http://ash.confex.com/ash/2009/webprogram/Paper22863.html

2679 Peripheral Blood Stem Cell Mobilization After Bendamustine Containing Chemotherapy in Indolent Lymphomas Is Possible. Results From the Phase III Study of B-R Vs. CHOP-R (NHL 1-2003 trial) of the StiL (Study group indolent Lymphomas, Germany)

Oral and Poster Abstracts
Poster Session: Lymphoma: Chemotherapy, excluding Pre-Clinical Models Poster II
Sunday, December 6, 2009, 6:00 PM-8:00 PM
Hall E (Ernest N. Morial Convention Center)
Poster Board II-655

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Introduction: Bendamustine, a hybrid alkylating agent, shows a unique mechanism of action with a good toxicity profile in various hematological malignancies, particularly in non-Hodgkin's lymphoma. Bendamustine (B) in combination with Rituximab (R) was demonstrated to be an effective regimen in first- or second-line treatment of patients (pts) with indolent lymphomas. So far, however, no data about the capacity of peripheral blood stem cell (PBSC) mobilization or a possible stem cell toxicity of B has been studied. It is still an open and clinically relevant question, if pts treated with B are able to mobilize enough stem cells for subsequent high dose therapy with autologous stem cell support.

Objective: We performed a prospective randomized multicenter phase-III trial to compare the efficacy and safety of the combination of Bendamustine plus Rituximab (B-R) versus CHOP plus Rituximab (CHOP-R) as first-line therapy for follicular, indolent and mantle cell lymphomas. Chemotherapy was given in 6 cycles each (B: 90 mg/m² d1+2). One of the secondary objectives (not mandatory) of this study was to evaluate the possibility to mobilize a sufficient number (at least 2.0 x 10E6 CD 34+ cells/kg) of PBSC and progenitor cells in younger pts after completing either B-R or CHOP-R and to compare both stem cells yields.

Results: 549 pts have been randomized, 513 pts (B-R = 260, CHOP-R = 253) are evaluable. In each arm, 23 PBSC mobilizations have been performed. In the B-R as well as in the CHOP-R arm each 18 mobilizations were performed directly after completion of therapy, and in 5 pts stem cells were collected at the time of first relapse. Patient characteristics: initial bone marrow involvement was observed in 17 of 23 pts in the B-R arm and 14 of 23 pts in the CHOP-R arm, respectively. Median patient age was 51 years (B-R) and 53 years (CHOP-R). The mobilization regimen was either high dose cyclophosphamide + G-CSF (9 pts in each arm) or G-CSF alone in 7 pts after B-R and in 2 pts after CHOP-R, respectively. Alternative regimens such as Dexa-BEAM, DHAP, ICE and others were also used in the remaining patients. The median CD34+ cell-count/kg was not significantly different in the two arms with 4.55 x 10E6 CD34+ cells/kg (range 1.68 – 12.35) in the B-R group and 6.17 x 10E6 CD 34+ cells/kg (range 1.68 – 20.39) in the CHOP-R group, respectively. In both arms the medium number of apheresis to achieve these yields was not different (B-R: 1.85 vs. CHOP-R: 1.66). Only 3 pts were not able to mobilize at least 2.0 x 10E6 CD 34+ cells/kg: 1 patient after B-R (1.68 x 10E6 CD 34+ cells/kg), and 2 pts after CHOP-R (1.68 x 10E6 CD 34+ cells/kg, and in 1 patient no mobilization was possible). In patients who were mobilized directly after completion of first-line chemotherapy (18 pts in each arm), again, no differences (B-R: median 5.52 x 10E6 CD 34+ cells/kg vs. CHOP-R: median 7.35 x 10E6 CD 34+ cells/kg) were observed. The yield of stem cells in each 5 pts of both arms who were mobilized at the time of first relapse was also nearly the same (B-R: median 8.79 x 10E6 CD 34+ cells/kg vs. CHOP-R: median 7.3 x 10E6 CD 34+ cells/kg).

Conclusions: Our results demonstrate that the collection of sufficient numbers of PBSC after B-R treatment is possible and appears to be comparable to the PBSC yield after prior treatment with CHOP-R.

Disclosures: Rummel: *Roche Pharma AG:* Honoraria, Research Funding; *Mundipharma:* Honoraria, Research Funding.

http://ash.confex.com/ash/2009/webprogram/Paper20787.html