9209 POSTER

Safety of romiplostim for treatment of severe chemotherapy induced thrombocytopenia (CIT) in patients with lymphoma receiving multi-cycle chemotherapy: results from an open-label dose- and schedule-finding study

M. Fanale[1], P. Stiff[2], K. Noonan[3], J. McCoy[4], M. Rutstein[3], C. Moskowitz[5]. *[1]MD Anderson Cancer Center, Lymphoma and Myeloma Center, Houston, USA; [2]Loyola University, Medical Center, Maywood, USA; [3]Amgen Inc., Hematology/Oncology, Thousand Oaks, USA; [4]Amgen Inc., Biostatistics, Thousand Oaks, USA; [5]Memorial Sloan Kettering Cancer Center, Division of Hematologic Oncology, New York, USA*

Background: Current treatment options for patients with CIT are limited and are associated with potentially serious risks. The primary objective of the current study was to identify a safe dose and schedule of romiplostim, a peptibody that increases platelet (PLT) production, in lymphoma patients receiving multi-cycle chemotherapy.
Methods: Eligible lymphoma patients experienced grade 3 or 4 thrombocytopenia (PLT count $<50\times10^9$/L) during a prestudy chemotherapy cycle. Patients received the same chemotherapy regimen (CHOP, ICE, or ESHAP with or without rituximab) during the first treatment cycle as during the previous qualifying cycle. A single subcutaneous injection of romiplostim (100, 300, 700, or 1000 μg) was administered 1 day after completing chemotherapy.
Results: Patient characteristics and safety and efficacy results are given in the Table. ECOG status was higher, and baseline PLT counts were lower, in the 700 and 1000 μg romiplostim groups. Use of specific chemotherapy regimens was not balanced between treatment groups. Adverse events (AEs) were consistent with those expected in lymphoma patients receiving multi-cycle chemotherapy. There was no dose-dependent effect of adding romiplostim to chemotherapy on the incidence of AEs or serious AEs when differences in baseline characteristics were accounted for. One patient with stage IV gastric lymphoma died (700 μg group) following a serious AE of gastrointestinal hemorrhage that was considered possibly related to romiplostim by the investigator. There was no evidence of a beneficial effect of romiplostim on the change in PLT nadir or other secondary efficacy endpoints.
Conclusions: Adding romiplostim to multi-cycle chemotherapy appeared tolerable in lymphoma patients with CIT. Further studies are warranted to explore different romiplostim doses and schedules including potential predosing before chemotherapy and multiple day dosing per cycle.

	Romiplostim				
	100 μg (N = 8)	300 μg (N = 11)	700 μg (N = 11)	1000 μg (N = 9)	Total (N = 39)
ECOG⩾1, n (%)	3 (38)	3 (27)	9 (82)	7 (78)	22 (56)
Baseline PLT $\times10^9$/L, mean (SD)	317 (162)	294 (208)	231 (79)	206 (78)	258 (142)
AEs, n (%)	6 (75)	9 (82)	8 (73)	9 (100)	32 (82)
Treatment-related AEs, n(%)	0	1 (9)	3 (27)	4 (44)	8 (21)
Serious AEs, n (%)	0	1 (9)	3 (27)	3 (33)	7 (18)
Serious treatment-related AEs, n(%)	0	0	1 (9)	0	1 (3)
PLT nadir change[A] $\times10^9$/L, median (range)	15 (−18, 55)	9 (−10, 61)	−4[B] (−16, 45)	−11 (−29, 48)	1 (−29, 61)

[A]From qualifying cycle to first romiplostim treatment cycle; [B]One patient in the 700μg group did not complete the first treatment cycle and was not included in efficacy analyses

ClinicalTrials.gov Identifier NCT00283439. Trial status: complete. Trial sponsor: Amgen Inc.

9210 POSTER

Bendamustine vs. fludarabine as second-line treatment in chronic lymphocytic leukemia

D. Medgenberg[1], L. Balleisen[2], W. Heit[3], W. Knauf[4], J. Weiβ[5], W. Freier[6], H. Eimermacher[7], S. Ibach[8], N. Niederle[1]. *[1]Klinikum Leverkusen, Hämatologie Onkologie und Palliativmedizin, Leverkusen, Germany; [2]Ev. Krankenhaus Hamm, Hämatologie und internistische Onkologie, Hamm, Germany; [3]Ev. Krankenhaus Essen-Süd, Innere Medizin Hämatologie und Onkologie, Essen, Germany; [4]Schwerpunktpraxis, Hämatologie und internistische Onkologie, Frankfurt, Germany; [5]Schwerpunktpraxis, Hämatologie und internistische Onkologie, Weiden, Germany; [6]Schwerpunktpraxis, Hämatologie und internistische Onkologie, Hildesheim, Germany; [7]Marien-Hospital, Hämatologie und Onkologie, Hagen, Germany; [8]Wissenschaftlicher Service Pharma GmbH, WiSP, Langenfeld, Germany*

Background: Bendamustine (B) demonstrated clinical activity in a wide range of pretreated hematological and non-hematological malignancies due to its unique mechanism of action distinct from classical alkylating agents reducing cross-resistance.
Material and Methods: Patients (pts) with relapsed CLL requiring treatment after one previous systemic regimen (usually chlorambucil-based, not including fludarabine (F) or B) were randomized centrally to either receive B 100 mg/m^2 as a 30-minute-infusion on days 1 + 2 of a 4week (w) cycle, or the "standard treatment" consisting of F 25 mg/m^2 on days 1 to 5 q 4w. Treatment was repeated until diagnosis of best response or up to a maximum of 8 cycles. The primary objective was to achieve comparable progression-free survival (PFS) to F in the treatment arm with B.
Results: Out of a total of 96 pts randomized between 2001 and 2006, 92 were eligible for the analysis, 49 allocated to B and 43 to F. B/F median age: 68/69 years, male pts: 63% in both arms, Binet C stage: 55/49%, B symptoms:41/38%, respectively. Bulky disease (11/14%) was equally distributed, while a favourable performance status was more frequent in the B group (43/29%). First-line treatment consisted of chlorambucil or the Knospe regimen in 96% of pts. About half of the pts received six or more cycles in either treatment arm. Overall response rates (ORR) were 78% (B) and 65% (F), clinical CR rates 29/10%. After a median follow-up of approximately three years and 79 events recorded, median PFS was 20.0/15.6 months (hazard ratio 0.87; 90% confidence interval: 0.59−1.28, p = 0.27). 24/26 pts have died after a median of 44/41 months (hazard ratio 0.82; 90% confidence interval: 0.51−1.30, p = 0.48). Hematotoxicity was marginally more frequent in the B arm, while non-hematological toxicities were generally rare, with B/F grade 3/4 infections of 13/15%, respectively. Conclusions: These data suggest at least comparable efficacy of B to F with respect to ORR, PFS and overall survival, pointing to an alternative treatment option to F in relapsing CLL pts after chlorambucil containing first line chemotherapy.

9211 POSTER

Dose dense R-CHOP-14 may be superior to conventional R-CHOP-21 with comparable toxicities in Asian patients with high risk Diffuse Large B Cell Lymphoma

W. Tai[1], I.B. Tan[1], M.Y. Tan[1], Y.Y. Ngeow[1], Y.X. Koo[1], M. Tao[1], R. Quek[1], S.T. Lim[1]. *[1]National Cancer Centre, Medical Oncology, Singapore, Singapore*

Background: Although the addition of Rituximab, to standard cyclophosphamide, doxorubicin, vincristine and prednisolone given every 21 days (R CHOP-21) significantly improves outcomes of patients with diffuse large B cell lymphoma (DLBCL) compared to CHOP-21 alone, about 40% of patients will relapse. Studies suggest that shortening the interval between chemotherapy cycles from 21 to 14 days increase dose intensity and may improve outcomes. This approach is not widely adopted, particularly in Asia, because of the impression that Asians tolerate dose-dense chemotherapy poorly. Further, the benefit of R-CHOP given every 14 days (R-CHOP-14) over R-CHOP-21 has not been demonstrated. This study aims to compare the safety and efficacy of R-CHOP-14 with R-CHOP-21.
Methods: Two hundred seventy five patients with DLBCL treated with curative intent from 2003 to 2008 were included: 52 received R-CHOP-14; 223 received R-CHOP-21.
Results: About 40% in each group had high risk disease, defined as the presence ⩾3 high risk factors (age > 60, high LDH, poor performance status, advanced stage and ⩾2 extranodal sites). After median follow up of 23 months, event free survival (EFS) was 87% and 73% for R-CHOP-14 and R-CHOP-21 respectively (HR 0.65, 95% CI: 0.8−1.5 p = 0.32). The overall survival (OS) was 93% and 79% for R-CHOP-14 and R-CHOP-21 respectively (HR 0.5, 95% CI: 0.15−1.6 p = 0.25). Among patients with high risk disease, R-CHOP 14 resulted in improvement in EFS (HR 0.24 95% CI: 0.08−0.085 p = 0.03). There is also significant improvement in OS (HR 0.13 95% CI: 0.02−0.96 p = 0.05). Toxicity profiles were similar in both arms; no treatment related mortality was reported. Therapy was delivered on time for dose-dense treatment arm in 88% of cycles.
Conclusion: This is the first report on R-CHOP-14 in Asians. R-CHOP-14 is safe and may confer an advantage in patients with high risk disease and should be evaluated in this group of patients, a study we are currently embarking.

9212 POSTER

Rituximab does not seem to influence the risk of central nervous system occurrence in patients with diffuse large B cell lymphoma

S. Chung[1], W.M. Tai[1], K. Ravi[1], I.B. Tan[1], M.Y. Tan[1], J. Ngeow[1], Y.X. Koo[1], M. Tao[1], R. Quek[1], S.T. Lim[1]. *[1]National Cancer Centre, Department of Medical Oncology, Singapore, Singapore*

Background: The introduction of Rituximab into the therapy of Diffuse Large B Cell Lymphoma (DLBCL) dramatically improved the prognosis.

However, relapse in the central nervous system (CNS) is still the issue. We studied the incidence, natural history, and risk factors predictive of CNS relapse in patients with DLBCL and evaluated the efficacy of Rituximab in preventing CNS relapse.
Methods: We conducted an analysis of CNS events on four hundred and sixty five patients with DLBCL treated in our institution from 2000−2008. 195 patients received CHOP chemotherapy and 270 patients received CHOP chemotherapy with Rituximab.
Results: The median age was 56 (range 17−91). The risk category by international prognostic index (IPI) was assessed as: low 42%, low intermediate 25%, high intermediate 19% and high 14%. After a median follow up period of 26 months, the cumulative incidence of CNS relapse was 3.9%. The median time from diagnosis to CNS relapse was 7.4 months (range 5−46 months). 89% of CNS relapse occurred within 1 year of diagnosis. Of the 18 patients with CNS relapse, 13 had isolated CNS relapse and 5 had concurrent systemic relapse. Patients with CNS relapse had a median survival of 4.4 months after relapse. Two year estimate of survival after CNS relapse was 6%. Significant differences in the incidences of CNS relapse were evident in patients with > I extranodal site of involvement, OR 2.14 (95% CI 1.24−3.70 $p = 0.017$), patients with stage 3 or 4 disease, OR 2.61 (955 CI 1.82–3.76 $p \leqslant 0.001$) and patients with high risk disease (IPI-high intermediate or high) OR 2.34 (95% CI 1.70−3.20 $p < 0.001$). There was no evidence that patients who received Rituximab had different rates of CNS relapse compared to patients who received only chemotherapy, 3% versus 5%, $p = 0.22$.
Conclusion: CNS relapse in patients with DLBCL is uncommon. CNS relapse almost always occur within 1 year of presentation, is usually isolated and predicts a poor prognosis. The number of extranodal sites, IPI score and stage at diagnosis were predictive of CNS relapse. There was no evidence however, to suggest that Rituximab decreases the risk of CNS relapse.

9213 POSTER

Induction and prolonged exposure to Rituximab in combination with Chlorambucil in untreated follicular lymphoma patients: a treatment with sustained response rate and a low toxicity profile

S. Bassi[1], S. Sammassimo[1], F. Gigli[1], E. Cocorocchio[1], P. Bertazzoni[1], L. Nassi[1], D. Laszlo[1], M.T. Lionetti[1], M. Negri[1], G. Martinelli[1]. *[1]European Institute of Oncology, Haematoncology Division, Milan, Italy*

Background: Rituximab in combination with chemotherapy improves outcome of follicular lymphoma (FL) patients with prolonged progression-free survival, overall response and median time to treatment failure compared to chemotherapy alone. However the natural history of the disease seems not influenced, so treatment options that extend the duration of remission with a low toxicity profile are warranted.
Material and Methods: Since December 2001 until September 2008 40 (18 male, 22 female) newly diagnosed FL patients (pts) received a combination of Rituximab and Chlorambucil (Chl). Rituximab was initially delivered with four week schedule in association with Chl (6 mg/sqm/daily) for 6 consecutive weeks. By 4−6 weeks all pts were valuated and, in the absence of disease progression, the treatment was prolonged with Rituximab once monthly and 14 days of Chl each month for 4 additional months.
Results: Median age at diagnosis was 56 years old (range 29−79). Twenty-nine pts had advanced stage of FL and the majorities (82%) were asymptomatic. Twenty-one pts (52%) were low risk FLIPI score. After the induction the ORR was 97% with 11 pts (27%) in complete response (CR). At the end of treatment 34 pts (85%) achieved a CR and 5 a PR. One patient presenting stable disease was subsequently treated with high dose chemotherapy and PBSC reinfusion. All pts but one concluded planned treatment. The mean daily dose of Chl received during the induction phase was 10 mg, while in the prolonged treatment was 9 mg. Seventeen pts (42%) required a dose reduction of Chl mainly in the prolonged phase because of haematological toxicity. No late toxicity has been observed. With a median follow up of 46 months (range 5−85) 29 pts (72%) maintain a CR. Eight pts relapsed and required a second-line treatment with a median time of 22 months (range 12−50).
Conclusions: Our results confirm that the prolonged exposure to monoclonal antibody Rituximab and Chl is safe and feasible. The schedule adopted with four additional Rituximab administrations improves clinical results observed with the standard weekly schedule, confirming the superiority of prolonged exposure to Rituximab. Our clinical results seem similar to those obtained with more aggressive therapies but with a lower degree of haematological and non haematological toxicities. In our opinion this combination may be suggested as first line treatment in management of FL patients, especially in those patients who prefer to avoid more aggressive chemotherapy regimens.

9214 POSTER

Interleukin-2 in combination with R-CHOP in the treatment of B-cell non-Hodgkin's lymphomas

N. Sachivko[1], E. Zhavrid[1], Y. Baranau[1], S. Petrovitch[1], I. Zhuravkin[1]. *[1]N.N. Alexandrov National Cancer Centre of Belarus, Chemotherapy, Minsk, Belarus*

Background: Experimental and clinical data suggest that the interleukin-2 (IL-2) increases the antibody-dependent cytotoxicity of rituximab (R). This cytotoxicity is one of the mechanisms of its antitumour activity. Simultaneous administration of these agents was supposed to contribute to an increase of effectiveness in treating B-cell non- Hodgkin's lymphomas (NHL).
Materials and Methods: 79 primary patients were enrolled in a randomized clinical trial. 42 patients received the standard R-CHOP regimen (arm A), 37 – the R-CHOP+IL-2 (Roncoleukin®, Biotech, Russia) regimen (arm B). IL-2 was administered daily subcutaneously in dose of 1 mg for 5 days during each chemotherapy course. The interval between courses was 21 days.
Results: The comparative assessment of results showed increasing efficacy of treatment in the arm B. Overall response rate (CR + mCR + PR) was 81.5% in the arm A and 91.9% in the arm B. The complete response rate was 63.1% and 75.6% in arms A and B respectively.
It was found that addition of IL-2 to standard R-CHOP regimen was effective in high risk group of patients (International Prognostic Index 3−5). Complete response rate in this group was 78.5% (arm B) versus 54.1% (arm A), $p < 0.05$. The follow-up period was from 6 months to 41 months. The median of event-free survival (EFS) was 22.9 months in arm A, and 30.9 months in arm B ($p = 0.5$).
Conclusions: Addition of interleukin-2 to the standard R-CHOP regimen for the management of B-cell non-Hodgkin's lymphomas seems to be associated with improvement of efficacy of treatment. The use of this regimen is justifiable for treatment of patients with a high risk of an unfavourable disease course (International Prognostic Index 3−5).

9215 POSTER

Treatment of previously untreated patients (pts) with AIDS-Related (AR) Non-Hodgkin's lymphoma (NHL) – a Cochrane systematic review

A. Martí-Carvajal[1], A.F. Cardona[2], A. Lawrence[3]. *[1]Iberoamerican Cochrane Network, Clinical Epidemiology and Public Health Department University of Carabobo, Valencia, Venezuela; [2]Catalan Institute of Oncology Hospital Germans Trias I Pujol, Medical Oncology, Barcelona, Spain; [3]Sanjay Gandhi Postgraduate Institute of Medical Sciences, Immunology, Lucknow, India*

Background: The incidence of NHL has increased about 100-fold in individuals infected with HIV. Previous studies have indicated that patients with AR-NHL have a poor prognosis. The use of HAART with different chemotherapy regimens improves outcome but there is still disagreement regarding the optimal treatment.
Methods: The Cochrane Library, MEDLINE, EMBASE, LILACS, Gateway and AIDSearch were used to identify registered randomized clinical trials (RCTs) assessing the effectiveness of systemic treatments for previously untreated AR-NHL pts. There were no age or language restrictions.
Results: The search strategy retrieved 1054 references but only 4 RCTs, with 857 pts treated with chemotherapy plus HAART, fulfilled the inclusion criteria (Kaplan 1991; Kaplan 1997; AMCT-010 2005; NHL-HIV-93 2006). Overall survival (OS) analysis: Kaplan 1997 (standard-dose m-BACOD+GM-CSF vs. low dose m-BACOD) reported a median OS of 35 and 31 wks for pts within low and standard dose respectively (HR 1.17, 95% CI 0.84−1.63; $p = 0.25$); AMCT-010 2005 (R-CHOP vs. CHOP) reported a median OS of 139 wks for R-CHOP and 110 wks for the CHOP group ($p = 0.76$); NHL-HIV-93 2006 reported no statistically significant differences for OS by any risk stratum (HIV score 0/ACVBP vs. CHOP: HR: 0.96, 95% CI 0.71−1.29, $p = 0.79$; HIV score 1/CHOP vs. low-dose CHOP: HR: 1.25, 95% CI 0.88−1.78, $p = 0.22$; HIV score 2−3/low-dose CHOP vs. VS: HR: 1.40 95% CI 0.89−2.20, $p = 0.14$). Disease-free survival (DFS) analysis: Kaplan 1997 reported a median DFS of 56 and 38 wks for the low-dose and standard-dose group respectively (HR 1.22, 95% CI 0.71−2.09; $p = 0.28$); AMCT-010 2005 did not evaluate this outcome and NHL-HIV-93 2006 reported a non-significant difference for DFS by any risk stratum.
Conclusions: Based on primary outcome analysis (OS/PFS) this systematic review did not found strong evidence to support the clinical effectiveness and safety of various chemotherapy approaches for AR-NHL, including those which evaluated the combination of HAART and rituximab with chemotherapy. There is a need for well-designed, adequately-powered randomized controlled trials in order to standardize and improve management of this clinical entity in patients with AIDS.