

2003

COS

Canadian Oncology Societies

December 6-9, 2003 San Diego, California

Conference Overview

The American Society of Hematology
45th Annual Meeting and Exposition



Canadian Oncology Societies

Overview of the 45th Annual Meeting and Exposition
of the American Society of Hematology

New Directions in Hematology Research and Clinical Practice

San Diego, California
December 6-9, 2003



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The Canadian Oncology Societies

This report has been produced as part of the continuing information program of the COS and attempts to provide a Canadian perspective to emerging data in oncology research and clinical practice. In particular, we wish to reflect highlights from The Annual Meeting of the American Society of Hematology, which will have a significant impact in Canada.

The report is also available on-line at the COS Webportal at www.cos.ca.

The Canadian Oncology Societies was founded in 1976. Over its nearly 30-year history, the mandate of the Canadian Oncology Societies has evolved, particularly in view of the development of specialty oncological associations.

The Canadian Oncology Societies has become a federation of oncological societies providing a common voice in oncology. The membership of the Canadian Oncology Societies includes the Canadian Association of Medical Oncologists (CAMO), the Canadian Hematology Society (CHS), the Canadian Society of Surgical Oncology (CSSO), the Society of Gynecologic Oncologists of Canada (GOC), the Canadian Association of Nursing in Oncology (CANO), and the Canadian Uro-Oncology Group (CUOG).

The Goals of COS

- Increase and exchange knowledge in the field of oncology.
- Promote the application of such knowledge in the prevention and diagnosis of cancer and the care of cancer patients and their families.
- Promote interdisciplinary approaches to patient care and research in cancer.
- Provide a forum for the presentation and discussion of scientific knowledge and advances in oncology.
- Advocate appropriate oncologic content in the curricula of universities, colleges and schools and in the programs of other training and educational bodies and organizations.
- Further continuing education for groups and individuals involved in the care of patients who require special attention. Support public cancer education programs.
- Support and assist the Canadian Cancer Society and the National Cancer Institute of Canada in their programs and activities and communicate and exchange information with other organizations interested in cancer.
- Advise government and other agencies on the provision of health services relevant to oncology.

We would certainly appreciate receiving your evaluation and suggestions following a review of this document. Please forward comments to info@cos.ca.

The Canadian Oncology Societies wish to thank Ortho Biotech for its unrestricted support of this publication and other COS education programs, including our webportal.

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Introduction

These proceedings present highlights of the main sessions of the 45th Annual Meeting of the American Society of Hematology (ASH) 2003, which review current concepts in hematology and the management of cancer. Several leading Canadian Hematologists provide a brief analysis of some of the most outstanding research presented at ASH and their relevance to Canadian research and clinical practice.

The 45th annual meeting of the American Society of Hematology (ASH) was, as every year, a platform for more than 20,000 clinicians and scientists from around the world to examine new and emerging trends and data for the screening, diagnosis and treatment of hematological disorders. While the majority of the outstanding posters, oral presentations and educational sessions centered on cancer treatment, researchers also presented data related to blood transfusion-related infection & safety, stem cell therapy and bone marrow transplants to cure diabetes.

A major topic reflected in many forums was the great advancement over the past decade in targeted cellular therapy in the treatment of cancer. Applying stem cell therapy, bone-marrow transplants and cloning, researchers are able to eliminate or replace diseased or dysfunctional cells and create healthy replacements.

This year Dr. Zhen-yi Wang of Shanghai became the first speaker from Asia to serve as the Ham-Wasserman Lecturer. In his manuscript entitled, "Treatment of Acute Leukemia by Inducing Differentiation and Apoptosis, Dr. Wang called on clinicians to apply Confucian thinking to cancer treatment, converting cancer cells rather than trying to defeat them.

Of significant interest were the following presentations:

- Identification of potential risk factors and promising new therapies for the treatment of thrombosis, including use of low-dose Aspirin® in patients with polycythemia (abnormal red cell counts)
- The therapeutic benefit of the first in-class proteasome inhibitor Bortezomib, also known as Velcade
- Impact of higher-dose kinase inhibiting imatinib (Gleevec®) and increased remission in the treatment of Chronic Myeloid Leukemia (CML)
- New therapies and screening recommendations for patients with anemia and Myelodysplastic Syndrome (MDS)
- Identification of genes which may help predict outcomes in childhood leukemia

As every year, the ASH annual meeting allowed Canadian researchers to demonstrate their considerable commitment and contribution to the greater understanding of disease prevention, and symptom and disease management. In fact, the Canadians were listed as authors or co-authors in 334 abstracts.

One of the notable contributions was an oral presentation on Hodgkins Disease by Dr. Ralph Myer, Hamilton Regional Cancer Centre and McMaster University. The presentation, which Dr. Silvy Lachance reviews herein, reported at year five of a twelve-year study on the long-term survival of patients with early-stage Hodgkins disease.

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Bortezomib Results

A major highlight of the American Society of Hematology Meeting was a series of reports describing quite remarkable therapeutic benefits of the first-in-class proteasome inhibitor bortezomib, also known as Velcade. It had been known that the ubiquitin proteasome pathway played an essential role in the degradation of most intracellular proteins and that at the heart of this degradative pathway is the 26S proteasome. It plays a vital role in degrading regulatory proteins that govern transcription factor activation, apoptosis, cell trafficking and the cell cycle. There were over 40 abstracts involving bortezomib in laboratory studies as well as a variety of clinical trials.

Abstract #512 described the characterization and reversibility of the peripheral neuropathy observed in the pivotal phase II trial of bortezomib in heavily pre-treated multiple myeloma patients. In that already published work, the response rate was 35%, leading to the approval of Velcade for that clinical indication. The follow-up work, though, carefully described the predominantly sensory neuropathy that has been reported in about 35% of patients. It was reported that the incidence of the neuropathy was increased in patients who had some underlying peripheral neuropathy at the time of entry into the study. The good news was that with dose reduction the neuropathy did not worsen. It also appeared to be reversible in the majority of cases once the therapy had been completed and the drug stopped.

[512] Peripheral Neuropathy Following Bortezomib (VELCADE™, Formerly PS-341) Therapy in Patients with Advanced Multiple Myeloma (MM): Characterization and Reversibility. Session Type: Oral Session

Paul G. Richardson, Hannah Briemberg, Sundar Jagannath, Bart Barlogie, James Berenson, Seema Singhal, Ann Traynor, David Siegel, David Irwin, Michael Schuster, Gordon Srkalovic, Raymond Alexanian, S. Vincent Rajkumar, Steven Limentani, Melissa Alsina, Robert Orlowski, David Kuter, Dixie Esseltine, Julian Adams, David P. Schenkein, Patrick Wen, Anthony Amato, Kenneth C. Anderson Dana-Farber Can Inst, Boston, MA, USA; St. Vincent's Comp Can Cen, NY, NY, USA; U AR Med Sci, Little Rock, AR, USA; Cedars-Sinai Med Cen, LA, CA, USA; Robert H. Lurie Can Cen, Chicago, IL, USA; Carol G. Simon Can Cen, Morristown, NJ, USA; Alta Bates Comp Can Cen, Berkley, CA, USA; NY Presby Hosp, NY, NY, USA; Cleveland Clin Found, Cleveland, OH, USA; MD Anderson Can Cen, Houston, TX, USA; Mayo Clin, Rochester, MN, USA; Carolinas Hem Onc Assoc, Charlotte, NC, USA; H. Lee Moffitt Can Cen Res Inst, Tampa, FL, USA; UNC Chapel Hill, Chapel Hill, NC, USA; Mass Gen Hosp, Boston, MA, USA; Millennium Pharm Inc, Cambridge, MA, USA

Bortezomib, a novel, first-in-class proteasome inhibitor, has recently been approved for the treatment of MM patients who have received at least 2 prior therapies and progressed on last therapy. The pivotal phase II trial (SUMMIT) enrolled pts with relapsed and refractory MM treated with 1.3 mg/m² of IV bortezomib twice weekly for 2 weeks in cycles given every 3 weeks. Responses were observed in 35% of the population, and included CR in 4%, near CR (100% disappearance of M protein by electrophoresis but positive for residual protein by immunofixation) in 6%, PR in 18%, and MR in 7%. The most common drug-related adverse events (incidence ≥ 30%) were nausea, diarrhea, fatigue, thrombocytopenia, and peripheral neuropathy (PN). CREST was a randomized phase II trial of 1.0 or 1.3 mg/m² of IV bortezomib administered in patients with relapsed or refractory MM, in which a similar response rate and toxicity profile were seen, with evidence of a possible dose effect. In both studies, sensory PN was reported as an important toxicity of bortezomib treatment and, in the pooled data from the SUMMIT and CREST MM trials (n=256), PN was reported to occur in 90/256 (35%) patients. Approximately 80% of patients entered these trials with evidence of PN as determined by patient completed questionnaires and neurologist examination. Of patients without PN, 3% (2/60) developed emergent grade 3 PN during treatment. Overall, dose reductions due to PN were required in 12% of patients, and 5% of patients discontinued drug due to PN. The incidence of grade 3 was increased in patients who had PN at baseline compared with those who did not (16% vs 3%). Follow-up analysis of the reversibility of PN in these patients is ongoing. Additional testing of a subgroup of patients by nerve conduction studies (NCS) and quantitative sensory testing (QST) showed results indicative of length-dependent axonal sensory polyneuropathy with predominant small fiber involvement. Detailed characterization on the subgroup of patients who had both NCS and QST will be presented together with data for all patients with PN on frequency, severity, and reversibility of bortezomib-associated PN.

Abstract #512 appears in Blood, Volume 102, issue 11, November 16, 2003

Interestingly, the renal complications that occur in multiple myeloma patients may not impede bortezomib therapy. This observation was described in Abstract #828 where the authors carefully analyzed the two prior phase II clinical trials of this agent and examined the outcome in patients who had severe renal impairment. They found that there were comparable response and discontinuation rates in patients with severe renal impairment, compared to with less severe renal impairment, and that comparable number of doses were able to be given. These findings have led to the study of the drug in severely impaired patients, including dialysis cases.

[828] Limited Experience from 2 Phase 2 Trials Suggests Bortezomib Can Be Given Safely in Multiple Myeloma (MM) Patients (pts) with Severe Renal Impairment with Comparable Responses and Toxicities. Session Type: Oral

Sundar Jagannath, Bart Barlogie, James Berenson, Seema Singhal, Raymond Alexanian, Gordon Srkalovic, Robert Orlowski, Paul G. Richardson, Darrell Nix, Roberto Guercioli, Dixie Esseltine, Kenneth C. Anderson, SUMMIT/CREST Investigators St Vincents Comp Can Cen, NY, NY, USA; U AR Med Sci, Little Rock, AR, USA; Cedars-Sinai Med Cen, LA, CA, USA; Robert H. Lurie Can Cen, Chicago, IL, USA; MD Anderson Can Cen, Houston, TX, USA; Cleveland Clin Found, Cleveland, OH, USA; UNC Chapel Hill, Chapel Hill, NC, USA; Dana-Farber Can Inst, Boston, MA, USA; Millennium Pharm, Cambridge, MA, USA

Introduction: Bortezomib was recently approved for pts with MM who have received ≥2 prior therapies and are progressing on last therapy. These pts often have renal impairment as a complication of disease or therapy. We retrospectively analyzed data from 2 phase 2 MM trials to determine if pts

with renal insufficiency can be treated with bortezomib with manageable toxicities. In nonclinical studies, bortezomib and its metabolites were eliminated by renal and hepatic routes. Pts with calculated creatinine clearances (CrCL; Gault-Cockcroft formula) of ≥ 30 mL/min were allowed to enroll, however, pts with CrCL < 30 mL/min could enroll with the Sponsor's approval. We were interested in the treatment experience of pts with severe renal impairment, and the relationship between degree of renal function and the bortezomib PK/PD.

Methods: The database for the SUMMIT and CREST phase 2 clinical trials (N=256) was reviewed to determine the number of pts who had impaired renal function when treated to assess their clinical characteristics, their response to and their tolerance of therapy with bortezomib. Results: There were 52 pts with calculated CrCL ≤ 50 mL/min, 99 in the 51-80 mL/min range and 105 in the > 80 mL/min group. The occurrence of Grade 3-4 adverse events (85%, 79%, 81%) and discontinuations (38%, 22%, 28%) from therapy were similar in the 3 groups. Ten pts of 256 were enrolled with calculated CrCL before therapy of ≤ 30 mL/min, with none requiring dialysis. Six started therapy at full dose, 1.3 mg/m², given biweekly for two weeks followed by a ten day rest period. Four started at 1 mg/m² on the same schedule. Responses to bortezomib alone determined by an independent review committee using the EBMT criteria showed that 2/10 had partial responses and 1 had a minor response. Most were able to tolerate therapy, 7/10 pts received 30 or more doses of a possible 32. Three discontinued therapy early (neuropathy, failure to thrive and pain). Limited PK data are available in another eight less severely affected pts from the SUMMIT trial. Their calculated CrCL ranged from 31-169 mL/min. The early bortezomib kinetic distribution (C_{max}, and distribution half-life) was not affected by renal status, while bortezomib systemic exposure (AUC) appeared similar to that obtained in the overall population. As observed in phase I studies, no correlation was found in phase 2 trials between the maximum 20S proteasome inhibition (1 hr post bortezomib) and various degrees of CrCL. Discussion and conclusions: Renal complications occur in MM pts but may not impede bortezomib therapy. We found that the 10 pts with severe renal impairment had comparable response and discontinuation rates as pts with less severe renal impairment, and were able to receive comparable number of doses. Although pts with impaired renal function may have more complications and adverse prognostic factors, many may be treated with benefit if closely monitored. Clinical experience in this population needs to be increased, and formal studies evaluating bortezomib PK/PD in severely impaired pts, including dialysis pts, are ongoing.

Abstract #828 appears in Blood, Volume 102, issue 11, November 16, 2003

Abstract #1629 tried to identify the prognostic factors that would predict for response and overall survival in multiple myeloma patients following treatment with bortezomib. In this analysis, the only prognostic factor that was associated with decreased duration of response time to tumour progression and reduced overall survival was high tumour burden. Interestingly, chromosome 13 deletion, beta2 microglobulin, the type and number of prior therapies were not predictors of duration of response, time-to-disease progression or overall survival. Perhaps the ongoing genomic analysis of the patient samples will ultimately turn out to be the key prognostic factor.

[1629] Prognostic Factors for Response Parameters and Overall Survival in Patients with Multiple Myeloma (MM) Following Treatment with Bortezomib. Session Type: Poster Session 741-I

Paul G. Richardson, Bart Barlogie, James Berenson, Seema Singhal, Sundar Jagannath, David Irwin, S. Vincent Rajkumar, Teru Hideshima, Barbara Bryant, George Mulligan, Hugh Xiao, Dixie Esseltine, David P. Schenkein, Kenneth C. Anderson, SUMMIT/CREST Investigators Dana-Farber Cancer Institute, Boston, MA, USA; U AR Med Sci, Little Rock, AR, USA; Cedars-Sinai Med Cen, LA, CA, USA; Northwestern Memorial Hosp, Chicago, IL, USA; St Vincent's Comp Can Cen, NY, NY, USA; Alta Bates Can Cen, Berkeley, CA, USA; Mayo Clin, Rochester, IL, USA; Millennium Pharm Inc, Cambridge, MA, USA

Introduction: The proteasome inhibitor bortezomib (VELCADE™) is a key regulator of protein homeostasis in cells, disruption of which can lead to cancer cell death. In SUMMIT, a phase II trial examining bortezomib efficacy and safety in 202 patients (pts) with relapsed and refractory MM, treatment (1.3 mg/m² 2x/wk x2 q3wk) induced a 35% overall response rate (RR). The most common ($> 30\%$) drug-related toxicities were nausea, diarrhea, fatigue, thrombocytopenia, and peripheral neuropathy. Prognostic factors (PF) associated with response to bortezomib in this study were previously reported. The current analysis focused on identifying potential PF for duration of response (DOR), time to disease progression (TTP), and overall survival (OS). Methods: PF for DOR, TTP, and OS were evaluated by separate univariate analyses using a Cox proportional hazards model, and a stepwise model selection procedure was used to determine the final multivariate analysis model. Factors assessed included age, gender, race, BSA, KPS, number of prior regimens, type of prior treatment, plasma cell infiltration of the bone marrow (PCBM), abnormal cytogenetics (inc. chromosome 13 deletion), B₂-microglobulin, albumin, hemoglobin, platelet count, C-reactive protein (CRP), and myeloma type. DOR and TTP were assessed for pts during treatment with bortezomib alone, while OS was assessed for all pts, during treatment with bortezomib \pm dexamethasone. Pharmacogenomic (PGX) analysis of enriched myeloma cells from pretreatment BM aspirates (with informed consent) in a subset of pts was used to assess response and TTP-associated gene expression.

Results: Prior multivariate analysis demonstrated that older age [32% RR in pts < 65 , 19% RR in pts ≥ 65 yrs] and $> 50\%$ PCBM [35% RR in pts with $\leq 50\%$ PCBM, 20% RR in pts with $> 50\%$ PCBM] was associated with a relatively lower response rate in SUMMIT (P < 0.05). Analysis focusing on DOR in CR/PR pts (n=53) showed that a shorter DOR was associated with lower levels of albumin (P=0.003) and a lower KPS (P=0.007). Overall, a shorter TTP was seen with $> 50\%$ PCBM (P=0.030), elevated CRP (P=0.025), or abnormal cytogenetics (P=0.047). OS was decreased with $> 50\%$ PCBM (P=0.040), lower platelet count (P=0.004), and lower levels of albumin (P=0.0002). Additional assessment included a Cox proportional hazards analysis of gene expression, which identified a significant number of genes correlated with TTP. Several of these genes, including those encoding cancer antigens and components of the ubiquitin/proteasome pathway, were identified in our earlier PGX analyses of response to bortezomib. Conclusions: PF associated with decreased DOR, TTP and OS in this analysis were associated with high tumor burden. Age ≥ 65 yrs, while predictive of lower response rates in a relapsed and refractory patient population, was not predictive of DOR, TTP, or OS. Other factors, including chromosome 13 deletion, B₂-microglobulin, and type or number of prior therapies were not predictors in any of these time to event analyses. PGX analysis and correlation with response and TTP is ongoing; ultimately, genomic approaches may offer a useful approach to prognosis.

Abstract #1629 appears in Blood, Volume 102, issue 11, November 16, 2003

There were several abstracts presented describing activity of bortezomib in lymphoma. Abstract #627 described a phase II study of relapsed or refractory indolent or aggressive lymphoma and noted that the highest response rate turned out to be in the mantle cell lymphoma subgroup where 8 of 15 evaluable patients responded. This is somewhat higher than the response rate observed in the Canadian study, Abstract #3358, which was restricted to just mantle cell lymphoma patients. In that report, 4 out of 12 patients responded to this therapy. The excitement for this first-in-class proteasome inhibitor, bortezomib is based on not only the current clinical trial results, but also the future potential. There were many pre-clinical studies describing how this agent could be used in combination with conventional chemo-therapeutic agents at much lower doses. Clinical trials are



already underway exploring those ideas, with the hope of observing synergistic cytotoxicity and improved patient outcome.

[627] Report of a Phase II Study of Proteasome Inhibitor Bortezomib (VELCADE™) in Patients with Relapsed or Refractory Indolent or Aggressive Lymphomas. Session Type: Oral Session

Andre Goy, Susan Hart, Barbara Pro, Peter McLaughlin, Anas Younes, Nam Dang, Luis Fayad, Jorge Romaguera, Fernando Cabanillas, Fredrick Hagemeister, Felipe Samaniego, Michael Wang, Ofelia Mesina, Frederic Gilles, Elizabeth Trehu, David Shenkein Lymphoma/Myeloma, M.D. Anderson Cancer Center, Houston, TX, USA; Millennium Pharmaceuticals, Cambridge, MA, USA

Background: The 26S proteasome plays a vital role in degrading regulatory proteins such as p53, p21, p27, NF- κ B, I- κ B, and bcl-2, that govern cell cycle, transcription factors activation, apoptosis and cell trafficking. Preclinical and phase I studies have suggested activity of the proteasome inhibitor bortezomib in B-cell indolent and aggressive lymphomas, especially in mantle cell lymphoma (MCL) patients.

Trial design: Bortezomib (VELCADE™, formerly PS-341) was given at 1.5mg/m² IV push on days 1, 4, 8 and 11 every 21 days. Restaging was done q2 cycles. Patients were treated for up to a total of 6 cycles unless removed from study for failure to respond or toxicity. Results: We have entered 30 pts to date on our trial including: 22 males, 8 females, median age 63 (range 45 to 79), 18 MCL, 12 other B-cell lymphomas including: 8DLCL (Diffuse Large Cell Lymphoma), 2FL (Follicular Lymphoma), 1 transformed FL, 1SLL (Small Lymphocytic Lymphoma). The number of prior therapies was as follows: 3.8 (range 1 to 8) for the entire group, 2.1 (range 1 to 5) in the MCL group and 4.3 (range 1 to 8) in the other patients, 7 pts had prior autologous stem cell transplant (ASCT): 3 MCL and 4 DLCL. Toxicity: A total of 63 cycles were given with an average of 2.1 cycles per patient (range 1 to 6). Main toxicities were as follows: GI: 5 pts had grade 3 or 4 nausea and /or vomiting or diarrhea; 4 pts had hypotension/fatigue/dehydration. Hematological toxicity: 6 pts had ANC<1000 but only one had <500 ANC. There were 2 infectious episodes: 1 pneumonia w/o neutropenia and 1 patient who developed generalized herpes zoster and died of encephalitis; 8 pts had platelets <20K but only 1pt<10K, there was no bleeding. 1 patient had grade 3 neuropathy (prior Vincristine and Taxanes). 4 pts developed transient rash (small vessel necrotizing vasculitis in 2 pts biopsied). Dose adjustment (dose minus 1) was required in only 3/29 pts. Response: In the MCL subgroup: we had 15 patients evaluable, 8/15 pts responded: with 3CR and 5PR for a RR of 53%. The duration of response was as follows: 1 patient with a CR had an ASCT 2 months later NED, the 2 other CR are NED 3 and 7 ms out; 5 PR had a median response duration of 3ms (range 1 to 11). Responses in other pts were as follows: 6/8 DLCL were evaluable whom 1/6 responded with a PR (RR 16%), 5 showed POD; 1 transformed FL was inevaluable, other pts did not respond. Conclusions: Bortezomib showed promising activity particularly in MCL (53% RR). In other subtypes of B-cell lymphomas, the RR was not as high but this was a more heavily pretreated population and most DLCL were primary refractory; we still had 1PR in a relapsed DLCL who had failed 4 prior therapies including an upfront autologous stem cell transplant. The main toxicity (fatigue, dehydration, hypotension) was manageable and improved with prophylactic routine IV hydration with bortezomib. Future directions will explore combinations with other chemotherapy and / or biological agents.

Abstract #627 appears in Blood, Volume 102, issue 11, November 16, 2003

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Non-Hodgkin's Lymphoma

At the plenary session, Dr. Thomas Habermann presented the results of an intergroup study comparing induction therapy with rituximab plus CHOP (R-CHOP) with the use of CHOP alone with a second randomization in patients achieving complete or partial remission to maintenance rituximab (MR) or observation. There was no difference in complete response rate (78% in patients treated with R-CHOP versus 77% in patients treated with CHOP). Time-to-treatment failure (TTF) defined as progression, relapse, death from any cause or institution of non-protocol therapy was improved by the use of R-CHOP as induction therapy; however, there was no difference in overall survival. When the entire group of patients that achieved a complete or partial remission with either R-CHOP or CHOP as induction was analyzed, there was no benefit to the use of MR. However, when the group of patients who had only received CHOP as their induction therapy was analyzed, there was a major improvement in TTF and overall survival in favour of MR. The use of MR confounds the analysis of the impact of using R-CHOP as induction therapy. When the patients who received MR are removed from the analysis, there then appears to be a significant improvement in TTF and a marginal improvement in overall survival with R-CHOP as induction. This analysis was not pre-planned; therefore, opinions vary on the significance of this study.

The lymphoma group from the BC Cancer Agency conducted a valuable analysis on the impact of adding rituximab to CHOP in patients with diffuse large B-cell lymphoma. They analyzed the patients who had presented before the provincial policy to recommend the addition of rituximab was implemented, and the patients presenting in the 18 months following implementation of the policy. Significant improvements in two-year progression-free survival and overall survival were observed.

[8] Phase III Trial of Rituximab-CHOP (R-CHOP) vs CHOP with a Second Randomization to Maintenance Rituximab (MB) or Observation in Patients 60 Years of Age and Older with Diffuse Large B-Cell Lymphoma (DLBCL). Session Type: Plenary Session

Thomas M. Habermann, E.A. Weller, V.A. Morrison, P.A. Cassileth, J.B. Cohn, S.R. Dakhil, R.D. Gascoyne, B. Woda, R.I. Fisher, B.A. Peterson,

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632 patients (pts) age ≥ 60 years with DLBCL were randomized to R-CHOP (318 pts) (cyclophosphamide 750 mg/m² IV Day 1, doxorubicin 50 mg/m² IV Day 1, vincristine 1.4 mg/m² (maximum dose=2) Day 1, prednisone 100 mg/m² Days 1-5, rituximab 375 mg/m² Day -7, -3, and two days before Cycles 3, 5, 7) versus CHOP (314 pts) for two cycles beyond CR (total 6-8 cycles). A second randomization to MR (207 pts) (rituximab 375 mg/m² weekly x 4 repeated every six months times four) versus observation (208 pts) was limited to the CR/PR pts. 540 pts were analyzable for induction and 348 for maintenance. The exclusion/ineligibility rate was 15%. Planned significance levels required for declaring a difference in time-to-treatment failure (TTF, defined as progression, relapse, death from any cause, institution of nonprotocol therapy) are 0.0230 for induction (87% information) and 0.0068 for maintenance (62% information). The median age was 69 years with no significant difference in clinical characteristics ($p > 0.50$). 26% of R-CHOP and 23% of CHOP pts had high-risk (international index 4, 5) disease. Overall response rates (ORR) were 77% R-CHOP and 76% CHOP ($p = 0.76$). Progressive disease (PD) during treatment occurred in 6.5% pts on R-CHOP and 10.5% pts on CHOP ($p = 0.12$). With a median follow-up of 2.7 years, the TTF favored R-CHOP for induction ($p = 0.025$), but there was no difference in overall survival (OS) ($p = 0.25$) (2-sided log rank p values). At six months and prior to the second randomization, the TTF failure rates were 15% for R-CHOP and 17% for CHOP ($p = 0.56$). TTF also favored MR ($p = 0.01$), but there was no difference in OS ($p = 0.67$). The interaction between induction and maintenance was analyzed. For R-CHOP pts, there was no significant difference between MR or observation for TTF ($p = 0.83$) or OS ($p = 0.33$). By contrast, CHOP pts had a significantly longer TTF with MR ($p = 0.0001$) but no statistically significant prolongation in OS ($p = 0.13$) to date. In interpreting these results and those from other studies, it is important to note that the current study was not designed to directly compare R-CHOP alone with CHOP alone. We conclude that the addition of rituximab to induction CHOP did not influence ORR or early (6 months) progression. However, induction R-CHOP (followed by MR or observation) did significantly prolong TTF. Maintenance rituximab also significantly prolonged TTF in responders, but this advantage appeared limited to patients induced with CHOP alone. At this time, no statistically significant differences in OS have been observed.

Abstract #8 appears in Blood, Volume 102, issue 11, November 16, 2003

Dr. Robert Marcus reported the results of a randomized trial evaluating the addition of rituximab to CVP chemotherapy in patients with previously untreated follicular lymphoma. The complete response rate was improved from 10% to 40% and the time-to-treatment failure was prolonged from 7 months to 27 months by the addition of rituximab.

[87] An International Multi-Centre, Randomized, Open-Label, Phase III Trial Comparing Rituximab Added to CVP Chemotherapy to CVP Chemotherapy Alone in Untreated Stage III/IV Follicular Non-Hodgkins Lymphoma. Session Type: Oral Session

Robert Marcus, Kevin Imrie, Andrew Belch, David Cunningham, Eduardo Flores, John Catalano, Philippe Solal-Celigny, Fritz Offner, Jan Walewski, João Raposo, Andrew Jack, Paul Smith (Intr. by Denis R. Miller) Department of Haematology, Addenbrookes Hospital, Cambridge, United Kingdom; Department of Hematology, Sunnybrook Regional Cancer Center, Toronto, Cape Verde; Department of Hematology, Cross Cancer Institute, Edmonton, Canada; Royal Marsden Hospital, Surrey, United Kingdom; Hospital Gregorio Marañon, Madrid, Spain; Monash Medical Centre, Clayton, Australia; Clinique Victor Hugo, Le Mans, France; U.Z., Dienst Haematologie, De pintelaan 185, Gent, Belgium; Lymphoma, M. Skłodowska-Curie Memorial Institute, Warszawa, Poland; Hospital Santa Maria, Lisboa, Portugal; Department of Pathology, Leeds General Infirmary, Leeds, United Kingdom; CRC and UCL Cancer Trials Centre, London, United Kingdom

Design/Methods: We present results of a phase III trial comparing the addition of rituximab to CVP chemotherapy to CVP alone in the therapy of previously untreated patients with stage III/IV CD20 positive follicular NHL. The regimens were cyclophosphamide 750mg/m² (day 1), vincristine 1.4mg/m² (day 1), and prednisolone 40mg/m² (days 1-5) (CVP) as a 21 day cycle for 8 cycles or the same regimen with rituximab- 375mg/m² on day 1 of each cycle (R-CVP). The major endpoint was time to treatment failure (TTF), defined as relapse, progression, stable disease after cycle 4, new anti-lymphoma treatment or death. Other endpoints of the study were time to progression (TTP), overall and complete response rates, duration of response, time to next therapy, disease free-survival and overall survival. Results: Between April 2000 and March 2002, 322 patients with a median age of 53 years (range 27-80) were recruited. 90% of patients had follicular small cell or follicular mixed NHL, and 9% follicular large cell NHL. According to the FLIP index 49% of patients had poor and 41% intermediate prognosis disease. Both regimens were well tolerated. The incidence of AEs was similar in both groups except for rituximab infusion related reactions in the R-CVP group. There were no differences in infection rates between the treatment arms and no treatment related deaths. The overall response rate (ORR) and complete response rate (CR + CRu) were 81% and 40% in the R-CVP arm vs 57% and 10% in the CVP arm respectively ($p < 0.0001$, Chi-square test for ORR). With a median follow-up of 18 months, R-CVP patients had a highly significantly prolonged time to treatment failure (TTF), median 27 months versus 7 months for CVP ($p < 0.0001$, log-rank test). The risk of an event was reduced by 66%. The median time to progression (TTP) has not yet been reached in patients receiving R-CVP compared to 13 months in those receiving CVP ($p < 0.0001$ log-rank test). The TTP in the CVP arm compares favourably with recently published data in a similar patient population. Conclusion: The combination of rituximab with CVP chemotherapy as first line treatment for advanced stage follicular NHL has significantly improved ORR and CR rates, TTF and TTP compared to CVP without any significantly increased toxicity. In our view the addition of rituximab to standard chemotherapy represents a major clinical advance for previously untreated patients with advanced stage follicular lymphoma.

Abstract #87 appears in Blood, Volume 102, issue 11, November 16, 2003

Two reports from the German low-grade lymphoma study group evaluated the addition of rituximab to chemotherapy in patients with previously treated and untreated follicular lymphoma. In the first study, Dr. Martin Dreyling reported the results of the study comparing the use of fludarabine, cyclophosphamide and mitoxantrone with the same drugs combined with rituximab in patients with previously treated follicular lymphoma. The addition of rituximab improved the overall response rate from 61% to 82% and improved the complete response rate from 14% to 37%. Progression-free survival was significantly higher in patients treated with rituximab added to the chemotherapy.

[351] Combined Immuno-Chemotherapy (R-FCM) Results in Superior Remission and Survival Rates in Recurrent Follicular and Mantle Cell Lymphoma - Final Results of a Prospective Randomized Trial of the German Low Grade Lymphoma Study Group (GLSG). Session Type: Oral Session



Martin H. Dreyling, Roswitha Forstpointner, Roland Repp, Sandra Hermann, Annette Haenel, Bernd Metzner, Christiane Pott, Frank Hartmann, Frank Rothmann, Reza Parwaresch, Michael Unterhalt, Wolfgang Hiddemann Department of Internal Medicine III, University of Munich - Hospital Grosshadern, Munich, Germany; Department of Internal Medicine III, University of Erlangen, Erlangen, Germany; Department of Hematology and Oncology, Robert Roessle Hospital, Berlin, Germany; Department of Internal Medicine III, Hospital Chemnitz, Chemnitz, Germany; Department of Internal Medicine II, Hospital Oldenburg, Oldenburg, Germany; Department of Internal Medicine II, University Hospital Schleswig-Holstein, Kiel, Germany; Department of Medicine I, University of Homburg/Saar, Homburg, Germany; Department of Hematology and Oncology, Ernst von Bergmann Hospital, Potsdam, Germany; Department of Hematopathology, University Hospital Schleswig-Holstein, Kiel, Germany

Rituximab monotherapy has shown a high activity in relapsed follicular lymphomas. In addition, phase II studies indicate that its addition to chemotherapy may further improve the response rate substantially. Thus, in 1998 the GLSG started a multicenter national trial in patients with relapsed or refractory follicular and mantle cell lymphoma. Since most patients had received CHOP for first line treatment, a fludarabine-containing regimen (FCM) was chosen for salvage therapy: fludarabine 25 mg/m² d 1-3, cyclophosphamide 200 mg/m² d 1-3, mitoxantrone 8 mg/m² d 1 every 28 days. A total of 4 courses were given. 147 Patients were prospectively randomized for FCM alone or FCM plus Rituximab (375 mg/m² on day 1, R-FCM). 65 of 126 evaluable patients (52%) had follicular, 48 patients (38%) mantle cell and 13 patients (10%) other indolent lymphomas. In patients treated with FCM alone 61% complete and partial remissions were observed (14% CR, 47% PR) whereas in the combined R-FCM arm, an overall response rate of 82% was obtained (37% CR, 46% PR; p<0.007). Similar improvement of remission rates were detected in follicular (94% vs. 74%) as well as in mantle cell lymphoma (62% vs. 43%). In the total group, the R-FCM arm was significantly superior concerning progression-free (p<0.028) and overall survival (p<0.002). Accordingly, in a subsequent subgroup analysis, progression-free survival in the R-FCM arm was higher in follicular lymphomas (p<0.014), and a significantly longer overall survival was observed in mantle cell lymphomas (p<0.005). In summary, this is the first prospectively randomized trial which demonstrates the superiority of a combined immuno-chemotherapy in patients with relapsed follicular and mantle cell lymphoma, both in terms of response rates but also in terms of survival.

Abstract #351 appears in Blood, Volume 102, issue 11, November 16, 2003

In the second study, Dr. Hiddemann reported the results of a randomized study in which 606 patients with previously untreated follicular lymphoma were randomized to CHOP alone or R-CHOP. R-CHOP led to a slight improvement in overall response (97% versus 93%) and complete response (21% versus 18%) but also demonstrated a major improvement in TTF. The TTF was 2.6 years in the CHOP arm and the TTF had not been reached in the R-CHOP arm. In a retrospective analysis, the survival rates of individuals treated with R-CHOP were equivalent to those treated with CHOP followed by peripheral stem-cell transplant in previous equivalent studies. Therefore, this group is now conducting a randomized study comparing CHOP followed by peripheral stem cell transplant with R-CHOP in this same group of patients.

[352] Combined Immuno-Chemotherapy (R-CHOP) Significantly Improves Time To Treatment Failure in First Line Therapy of Follicular Lymphoma Results of a Prospective Randomized Trial of the German Low Grade Lymphoma Study Group (GLSG). Session Type: Oral Session

Wolfgang Hiddemann, Martin H. Dreyling, Roswitha Forstpointner, Michael Kneba, Bernhard Woermann, Eva Lengfelder, Rudolf Schmits, Marcel Reiser, Bernd Metzner, Norbert Schmitz, Lorenz Truemper, H. Eimermacher, Reza Parwaresch Department of Internal Medicine III, University of Munich - Hospital Grosshadern, Munich, Germany; Department of Internal Medicine II, University Hospital Schleswig-Holstein, Kiel, Germany; Department of Internal Medicine, Hospital Braunschweig, Braunschweig, Germany; Department of Internal Medicine III, University of Heidelberg - Hospital Mannheim, Mannheim, Germany; Department of Internal Medicine I, University Hospital Homburg/Saar, Homburg, Germany; Department of Internal Medicine I, University Hospital Cologne, Cologne, Germany; Department of Internal Medicine II, Hospital Oldenburg, Oldenburg, Germany; Department of Internal Medicine, St. Georg Hospital, Hamburg, Germany; Department of Internal Medicine, University Hospital Goettingen, Goettingen, Germany; Department of Medicine, St. Marien Hospital, Hagen, Germany; Department of Hematopathology, University Hospital Schleswig-Holstein, Kiel, Germany.

The chimeric anti-CD20 antibody rituximab has shown a high activity in the treatment of follicular lymphoma. Initial phase II studies also suggested that its addition to chemotherapy may further improve the response rates substantially. Based on these encouraging clinical results and the observed in vitro chemosensitizing effect of the antibody, the German Low Grade Lymphoma Study Group (GLSG) initiated a prospective randomized phase III study to evaluate the efficacy of a combined immuno-chemotherapy in first-line treatment of lymphoma. Since May 2000, a total of 606 patients were randomly assigned to receive either up to 6 courses of a standard CHOP chemotherapy (cyclophosphamide 750 mg/m² d1; doxorubicine 50 mg/m² d1; vincristine 1.4 mg/m² d1; prednisone 100 mg/m² d1-5) or a combined immuno-chemotherapy (CHOP+Rituximab 375 mg/m² d1). Responders subsequently underwent an interferon-alpha maintenance therapy or a myeloablative consolidation followed by autologous stem cell transplantation. In 394 currently evaluable patients with follicular lymphoma, the addition of rituximab led only to a moderate improvement of CR rate (21% vs. 18%) and overall response (97% vs. 93%) in comparison to chemotherapy alone. However, time-to-treatment failure (TTF) on follicular lymphomas was significantly increased after combined immuno-chemotherapy (p<0.0007). Estimated median TTF was 2.6 years in the CHOP arm, whereas after a maximum follow-up of nearly three years it is not reached for R-CHOP. Toxicity in both treatment arms was comparable with only a slight increase of grade III/IV neutropenia (42% vs. 37%) and allergy-like symptoms (4% vs. 0%) in the R-CHOP arm. In summary, the addition of rituximab to CHOP chemotherapy resulted in a significant increase of time to treatment failure and thus may represent the new standard therapeutical approach in first-line treatment of follicular lymphoma.

Abstract #352 appears in Blood, Volume 102, issue 11, November 16, 2003

Other studies focused on the addition of rituximab to bendamustine in patients with relapsed or refractory indolent and mantle cell lymphomas. Bendamustine has been used in East Germany for the treatment of lymphoma for many years. Complete responses were seen in 71% of patients with follicular lymphoma, 50% of patients with mantle cell lymphoma, 64% of patients with immunocytoma and all 4 patients with marginal zone lymphoma. A randomized study comparing bendamustine plus rituximab with R-CHOP has been instituted.

The South West Oncology Group presented a phase 2 trial of CHOP followed by Tositumomab/iodine-131 then Tositumomab again (BEXXAR) in patients with newly diagnosed follicular non-Hodgkin's lymphoma. Extremely high response rates were seen which has led to the phase 3 study, comparing the combination with use of CHOP alone in patients with follicular lymphoma.

[90] CHOP Followed by Tositumomab/Iodine I 131 Tositumomab (BEXXAR®) for Treatment of Newly Diagnosed Follicular Non-Hodgkin's Lymphomas: A Phase II Trial of the Southwest Oncology Group (S9911). Session Type: Oral Session

Oliver W. Press, Joseph M. Unger, Rita M. Braziel, David M. Maloney, Thomas P. Miller, Michael LeBlanc, Richard I. Fisher, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; Southwest Oncology Group Statistical Center, Seattle, WA, USA; Oregon Health Sciences University, Portland, OR, USA; Arizona Cancer Center, University of Arizona, Tucson, AZ, USA; James P. Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY, USA

Advanced follicular lymphomas are incurable with conventional chemotherapy regimens. The Southwest Oncology Group investigated the safety and efficacy of a novel treatment approach by administering 6 cycles of CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) given at 3 week intervals followed by radioimmunotherapy. Four weeks after the completion of the last cycle of CHOP, patients with a partial (PR) or complete remission (CR) to chemotherapy underwent dosimetry with 450 mg of unlabeled Tositumomab antibody followed by 35 mg of Tositumomab trace-labeled with 5 mCi of Iodine-131. Based on the rate of clearance of this dosimetric infusion from the body, as assessed by gamma counting, subjects were treated 1-2 weeks later with unlabeled Tositumomab followed by Tositumomab labeled with 48-115 mCi of I-131 (median 84.5 mCi) to deliver 75 cGy to the whole body (or 65 cGy if the platelet count was 100,000-149,999). 102 patients with newly-diagnosed follicular lymphomas (grade 1, 2, or 3) were registered by the time of study closure on June 1, 2000 and 90 were eligible. Preliminary results of the first 71 evaluable patients were presented at ASH, 2001 (abstract # 3504); we now report an update including all 90 eligible patients followed for a median of 2.7 years after registration. 89 patients are evaluable for toxicity from the CHOP regimen and 35 grade 4 toxicities were observed due to CHOP, including 32 (36%) with grade 4 hematologic toxicities. 83 patients are evaluable for toxicity from the BEXXAR® therapeutic regimen. 10 patients (12%) experienced 13 grade 4 toxicities (neutropenia in 5, leukopenia in 2, thrombocytopenia in 2, anemia in 2, one anaphylactoid reaction and chest and back pain in one). One case of myelodysplasia, one case of breast cancer, and seven cases of elevated thyroid stimulating hormone levels have been observed. There were no treatment-related deaths. Of the 90 eligible patients, 82 (91%) have achieved an objective remission, including 51 confirmed CRs (57%), 11 unconfirmed CRs (CRu) (12%), and 20 PRs (22%). Two patients had stable disease (2%) and 6 patients had inadequate data for response assessment (7%). Among the 47 fully assessable patients with a PR or CRu to CHOP for whom response data is available after each stage of the regimen, the addition of BEXXAR improved overall response in 28 patients (60%), either from a PR to a CRu or CR (n=24) or from a CRu to a CR (n=4). The 2-yr estimates of overall and progression-free survival are 97% and 81%, respectively. We conclude that the addition of the BEXXAR therapeutic regimen to 6 cycles of CHOP chemotherapy is feasible, well-tolerated, and efficacious and that the therapeutic results exceeded our expectations based on historical experience with CHOP alone (PFS = 65% and OS = 91% at 2 yr). SWOG and CALGB are currently conducting a prospective randomized study (S0016) comparing CHOP + BEXXAR to CHOP + rituximab.

Abstract #90 appears in *Blood*, Volume 102, issue 11, November 16, 2003

The German CLL study group reported results of a study comparing the use of fludarabine, with cyclophosphamide plus fludarabine, as first-line therapy in patients with chronic lymphocytic leukemia (CLL) requiring treatment. The overall response rate (94.2%) and complete response rate (20.2%) were significantly higher for patients treated with fludarabine plus cyclophosphamide than for patients treated with fludarabine alone (overall response rate 85.7%, complete response rate 8.6%). The progression free survival was slightly longer in the fludarabine plus cyclophosphamide group (28.2 months) compared to the fludarabine alone group (22.8 months). This led to a major difference in event free survival.

[243] Fludarabine Plus Cyclophosphamide (FC) Induces Higher Remission Rates and Longer Progression Free Survival (PFS) than Fludarabine (F) Alone in First Line Therapy of Advanced Chronic Lymphocytic Leukemia (CLL): Results of a Phase III Study (CLL4 Protocol) of the German CLL Study Group (GCLLSG). Session Type: Oral Session

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Introduction: F is the most effective monotherapy for CLL. Combining F with other cytotoxic agents may further improve the quality of the response to treatment and prolong survival. FC is particularly promising, since it achieves response rates of >90% with up to 46% complete remissions (CRs) in patients (pts) with untreated CLL. To evaluate the potency of the FC combination, the GCLLSG has initiated a phase III study to directly compare the safety and efficacy of F vs. FC as first-line therapy for advanced CLL.

Patients: 375 pts (mean age 56.5 [range 37-65] years) were randomized to receive either F (n=190) or FC (n=185). 24 pts were in Binet stage A with severe symptoms requiring therapy, 183 in stage B, and 108 in stage C. This analysis was performed with all information available as of August 2003. Staging data were not yet available for 60 pts. Pts in the FC arm received F (30 mg/m²/day (d) IV) plus C (250 mg/m²/d IV) for 3 consecutive days, every 28 days for up to 6 cycles. Pts in the F arm received F (25 mg/m²/d IV) for 5 consecutive days, every 28 days for up to 6 cycles. Anti-infective prophylaxis and growth factors were not given routinely. So far, pts in the F arm had received a median of 4.9 courses vs. 4.8 courses in the FC arm.

Results: 209 pts were evaluable for response. The overall response rate (ORR) was significantly higher in pts treated with FC (98/104; 94.2%) than pts treated with F alone (90/105; 85.7%) (p=0.041). The CR rate was significantly higher with FC therapy than with F (20.2% vs. 8.6%) (p=0.017). After a median follow-up of 11.65 months (mo) 87/103 (84.5%) pts in the FC arm vs. 72/104 (69.2%) in the F arm remained in remission. The median duration of response has not yet been reached in both arms. In a preliminary analysis, significant difference in the progression-free survival (PFS) of 28.2 mo in the FC arm vs. 22.8 mo in the F arm was observed. 240 pts were evaluable for safety. Side-effects were significantly more frequent with FC than with F: 80.5% vs. 56.8% of 550 and 597 courses, respectively, showed some side-effects (p<0.001). In particular, myelosuppression was significantly more frequent (66.9% vs. 39.7%; p<0.001) and more severe in the FC arm (25.6% vs. 12.8% common toxicity criteria (CTC) grade 3+4; p<0.001). Leukocytopenia was also more frequent (60.1% vs. 32.3%; p<0.001) and severe (22.3% vs. 7.8% CTC grade 3+4; p<0.001) in the FC arm. Thrombocytopenia was more frequent in the FC arm as well (23.6% vs. 14.2%; p<0.001). In marked contrast, anemia was more severe in the F arm (5.6% vs. 1.8%; p=0.001). The incidence of severe infections was similar in both arms (2.0% vs. 2.0% p=0.985). There were two treatment-related deaths in the FC arm and three in the F arm, due to autoimmune haemolytic anaemia, autoimmune thrombocytopenia, neutropenic sepsis and tumour lysis syndrome.

Conclusion: FC induces a significantly higher ORR and CR rate than F. Moreover, the PFS seems also to be longer after FC. Though leukocytopenia was more frequent and severe with FC, the incidence of infections was similar in both arms. Due to these results, the GCLLSG will use FC as the “standard” first-line treatment in future trials on younger CLL pts.

Abstract #243 appears in Blood, Volume 102, issue 11, November 16, 2003

A North American Intergroup CLL study compared the use of fludarabine alone with the use of fludarabine combined with rituximab in patients with previously untreated CLL who required therapy. Both the complete remission rate (38% versus 20%) and the complete plus partial remission rate (84% versus 63%) were significantly better in the fludarabine plus rituximab treated patients. The 2-year progression-free survival was 67% in the rituximab plus fludarabine treated group and 45% in the fludarabine treated group. There was a statistically significant improvement in overall survival (93% versus 81%) with the addition of rituximab to the fludarabine therapy.

[244] ZAP-70 Protein Expression Varies by Interphase Cytogenetic Group and May Predict Disease Progression to Requirement of Treatment among Select Genetic Groups in Patients with Chronic Lymphocytic Leukemia (CLL). Session Type: Oral Session

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B-cell CLL is characterized by several different genetic abnormalities including del(11)(q23), del(17)(p13.1) and p53 mutations that are highly predictive of rapid disease progression (DP) and inferior overall survival (OS). The lack of immunoglobulin VH gene mutations, and the surrogate marker ZAP-70 expression, also have been identified to predict for rapid DP and inferior OS. As part of a Phase III NCI intergroup study of previously untreated CLL patients who uniformly met the NCI 96 criteria for treatment and were randomized to receive fludarabine or fludarabine plus cyclophosphamide, we sought to determine the time from diagnosis to DP based upon cytogenetic group and ZAP-70 expression and whether expression of ZAP-70 among similar interphase cytogenetic groups could predict varied outcome. To date, we have completed analysis of multiple parameters including interphase cytogenetics on 176 patients, and ZAP-70 protein was quantified on 105 patients by immunoblot analysis. Interphase cytogenetic groups were prioritized as follows (17p-/p53 mutated > 11q- > 6q- > tri12 > normal > 13q-). Medians for time from initial diagnosis to treatment and for ZAP-70 protein quantitation are given in the first table.

	17p-	11q-	6q-	Trisomy 12	Normal	13q-
n=	18	31	7	34	30	56
Median Time to DP (range)	14 mo. (0-72)	13 mo. (0-87)	0.6 mo. (0-17)	23 mo. (0-101)	13 mo. (0-97)	25 mo. (0-150)
Median Ratio ZAP - 70:GAPDH	0.335 (n=10)	0.335 (n=18)	0.625 (n=4)	0.16 (n=21)	0.59 (n=17)	0.10 (n=35)

ZAP-70 expression as demonstrated in this analysis was significantly associated with cytogenetic group (p=0.00009). Time from diagnosis to DP was moderately associated with cytogenetics (p=0.06). To further explore the impact of ZAP-70 expression among different cytogenetic groups, we separated groups who had data for both assessments. ZAP-70 was dichotomized based upon expression above or below the median value quantified by immunoblot analysis in the second table.

		17p-	11q-	Trisomy 12	Normal	13q-
ZAP-70:GAPDH Ratio > 0.30	median DP (n)	16 mo. (5)	11 mo. (9)	36 mo. (4)	22 mo. (13)	20 mo. (5)
ZAP-70:GAPDH Ratio ≤ 0.30	median DP (n)	29 mo. (5)	26 mo. (9)	23 mo. (17)	14 mo. (4)	24 mo. (30)

Our data suggests that assessment of ZAP-70 protein expression levels in untreated CLL patients varies by interphase cytogenetic group, and is highly associated with time from diagnosis to onset of treatment ($P=0.00001$). Although the number of patients with 6q- is small, they had a short median time from diagnosis to treatment with high values for ZAP-70. Furthermore, in select high risk groups (17p- & 11q-) where progression is heterogeneous, ZAP-70 may also distinguish patients who have a predisposition to early versus late DP. ZAP-70 determinations in patients with CLL complement cytogenetic data, and will assist in planning therapeutic decisions. Relationship to IgV_H mutational status on this patient population will be reported. This study is supported by National Institutes of Health R01 CA88647 to MRG.

Abstract #244 appears in Blood, Volume 102, issue 11, November 16, 2003.

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Erythropoietin Therapy

There were several presentations relating to erythropoietin therapy, whose themes were common: the benefit for patients receiving EPO, and the impact on tumour response and overall survival which remain open questions.

Abstract #709 is a meta-analysis of interest, since it includes a total of 27 trials. No comment was made on why an additional 6 studies were deemed eligible but were not included. The general message is that EPO reduces transfusion requirements predominantly in patients with solid tumours, without improving the anti-tumour response. A trend to improved survival was mentioned. Not discussed was the topic of a negative effect of EPO on tumour response.

[709] Does Erythropoietin Improve Overall Survival in the Treatment of Patients with Malignant Diseases? Results of a Comprehensive Meta-Analysis. Session Type: Oral Session

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Background: Cancer and cancer therapy associated anaemia may have an impact on tumor response and overall survival (OS). Additionally, anaemia represents an important economic factor. Therefore, therapeutic alternatives such as erythropoietin (EPO) and red blood cell transfusions have to be evaluated systematically.

Objectives: To determine the effectiveness of recombinant human erythropoietin to prevent or alleviate anaemia in patients (pts) with malignant disease.

Methods: Randomised controlled trials comparing prophylaxis or treatment of anaemia with EPO and red blood cell transfusion (RBCT) or RBCT only in pts with malignant disease undergoing antineoplastic therapy were included. Endpoints included the need for RBCT, hematological response (hemoglobin increase of 2 g/dL or hematocrit increase of 6% points), tumor response and overall survival. Medical databases (Cochrane Library, MEDLINE, EMBASE) and conference proceedings were searched (1985-2001). We included full-text and abstract publications as well as unpublished data. Data extraction and quality assessment were done in duplicate. All authors were contacted to obtain missing data.

Main results: Out of 33 eligible studies, 27 trials with 3,284 randomised pts were included. Application of EPO significantly reduced the relative risk to receive red blood cell transfusions (RR 0.67 [95% CI 0.62-0.73], 24 trials, n=2,923). Pts with solid tumors had a more pronounced decrease in transfusion risk (RR 0.49 [95% CI 0.41-0.59], 13 trials, n=1,094) than pts with hematological malignancies (RR 0.77 [95% CI 0.67-0.87], 5 trials, n=966) or MDS (RR 0.80 [95% CI 0.68-0.96], 2 trials, n=151). Hematological response was observed in 690/1,338 (52%) pts in the EPO group compared to 142/1,009 (14%) pts in the control group (RR 3.60 [95% CI 3.07-4.23], 14 studies, n=2,347). There was no evidence for EPO to improve tumor response (RR 1.36 [95% CI 1.07-1.72], 7 studies, n=1,150) and a trend to improve overall survival (HR 0.80 [95% CI 0.65-1.00], 8 trials, n=1,624).

Conclusion: EPO given during antineoplastic therapy in pts with malignant disease reduces the relative risk for the need of red blood cell transfusion and augments the relative risk to achieve hematological response. However, more clinical trials are needed to test the hypothesis that EPO may indeed improve OS.

Abstract #709 appears in Blood, Volume 102, issue 11, November 16, 2003

Abstract #4368 which concerned the effect of EPO in geriatric patients was examined in retrospective, multi-centre efficacy studies. EPO was administered 3 times weekly. The data were compared to data from a group of younger patients. Both showed a reduction in transfusion requirement with similar hematological response rates. QOL improvements were better in younger patients. The differences comparing the groups do not seem to be substantial, thus suggesting the use is independent of age. A statement with respect to side effects and tolerance of EPO for both groups would have been desirable.

[4368] Epoetin Alfa Improves Hemoglobin and Quality of Life in Anemic Geriatric Cancer Patients ≥ 60 Years Receiving Chemotherapy. Session Type: Publication Only

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Publication Only

Background: Anemia is common and an important prognostic predictor in geriatric cancer patients. To evaluate the use of epoetin alfa to treat anemia in this patient population, we conducted a retrospective subgroup analysis of anemic geriatric cancer patients (age ≥ 60 years) receiving chemotherapy who participated in 3 community-based effectiveness studies of epoetin alfa. Study design: Analyses were conducted based on the overall population of geriatric patients (age ≥ 60 years) and by geriatric age groupings (60-64, 65-69, 70-74, 75-79, 80-84, ≥ 85 years), as well as compared with younger patients (age < 60 years), from the individual studies and across pooled study data. In the thrice weekly dosing studies, patients initially received epoetin alfa 150 U/kg or 10,000 U subcutaneously (SC), with doubling of the dose if hemoglobin (Hb) increase was ≤ 1 g/dL after 4 weeks. In the weekly dosing study, patients initially received epoetin alfa 40,000 U SC, with dose escalation to 60,000 U if Hb increase was ≤ 1 g/dL after 4 weeks. For all 3 studies, maximum treatment duration was 4 months. Results: A total of 4572 geriatric patients (age ≥ 60 years) and 2541 younger patients (age < 60 years) participated in the 3 studies (mean age 71.0 ± 6.6 years for geriatric patients vs 48.8 ± 8.6 years for younger patients). 58% of geriatric patients and 70% of younger patients were female. Most patients in both the geriatric and younger subgroups had solid tumors (78% and 85%, respectively); the most common tumors were lung (27%, 19%), breast (13%, 28%), gastrointestinal (13%, 11%), and gynecologic (13%, 15%). From baseline to final measurement, epoetin alfa therapy significantly ($P < .0001$) increased Hb by 2.0 g/dL in patients ≥ 60 years and by 1.9 g/dL in patients < 60 years. Transfusion utilization was significantly reduced in both groups ($P < .006$). QOL improvements from baseline, measured by the 100-mm Linear Analog Scale Assessment (LASA), were clinically meaningful and significant in both age groups. In geriatric patients, mean changes from baseline in LASA scores (mm) were +11.8 for Energy, +10.4 for Activity, and +9.0 for Overall QOL ($P < .05$). Mean LASA improvements from baseline for the same QOL measures in younger patients (+14.3, +13.6, and +11.5, respectively) were significantly greater than those in geriatric patients ($P < .05$, between groups). No significant differences were observed across any geriatric age subgroup evaluated or between the thrice weekly and once weekly regimens for Hb change and QOL improvement. Overall hematologic response rate (defined as a ≥ 2 g/dL increase in Hb or Hb ≥ 12 g/dL, independent of transfusion) was 65.5% for geriatric patients and 64.9% for younger patients. Significant predictors of hematopoietic response to epoetin alfa in the geriatric population included lower body mass index/weight, reduced baseline endogenous serum erythropoietin levels, better tumor response, and history of epoetin alfa dose decreases or stable dose. Conclusions: These data suggest that anemic geriatric cancer patients receiving chemotherapy respond similarly to epoetin alfa as younger patients and should be treated as intensively to optimize their outcomes. Both age groups achieved significant improvements in Hb and QOL, although QOL improvements were generally somewhat greater in younger patients. There appeared to be no appreciable difference in either Hb or QOL responses to epoetin alfa for geriatric patients of any age subgroup.

Abstract #4368 appears in Blood, Volume 102, issue 11, November 16, 2003

Abstract #4375 was an open-label, non-randomized multi-centre study that tested the effect of once weekly administration of EPO on the hematological response, transfusion requirements and QOL of patients with malignancies, not receiving concomitant chemotherapy or radiation. Improvement was observed for all study parameters. The critique of this abstract is the low number of evaluated patients. The other concern is the fact that the interim analysis may introduce a bias into the enrolment of future patients. The endpoint of enrolment was not critically stated.

[4375] Epoetin Alfa 40,000 U Once-Weekly (QW) Increases Hemoglobin (Hb) and Improves Quality of Life (QOL) in Anemic Patients with Cancer Not Receiving Chemotherapy (CT) or Radiation Therapy (RT). Session Type: Publication Only

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Publication Only

Patients (pts) with cancer often develop anemia as a consequence of cytotoxic therapy or the disease itself. Cancer-related anemia may be due to anemia of chronic disease or may be the result of blood loss, nutritional deficiencies, or tumor infiltration of bone marrow. In studies of anemic pts with cancer receiving CT, epoetin alfa significantly increased Hb levels by ~ 1 g/dL in 4 weeks and ~ 2 g/dL in 8 weeks, decreased transfusion utilization, and improved QOL. The current open-label, nonrandomized, multicenter, pilot study is evaluating the efficacy and safety of epoetin alfa administered once-weekly (QW) in 100 anemic pts with cancer not receiving CT or RT. The primary efficacy variable is hematologic response (independent of transfusions within 28 days) from baseline to week 13. Secondary efficacy variables include transfusion utilization and QOL measured by the 100-mm Linear Analog Scale Assessment (LASA). Eligible pts must be ≥ 18 y, be diagnosed with a nonmyeloid malignancy, have an ECOG performance status (PS) 0-2, and have Hb ≥ 11 g/dL. Exclusion criteria include receipt of CT within 8 weeks or RT within 4 weeks of enrollment, red blood cell transfusion within 28 days of enrollment, or RT to $> 25\%$ of bone marrow reserve. The starting dose of epoetin alfa is 40,000 U administered SC QW. Treatment duration is up to 12 weeks with a 4-week posttreatment observation period. If Hb increases < 1 g/dL after 4 weeks, the dose is increased to 60,000 U QW. The dose of epoetin alfa will be reduced for Hb > 15 g/dL and a dose reduction considered for Hb increase > 1.3 g/dL over 2 weeks. 67 pts have been enrolled to date. Preliminary data from 29 pts (mean age, 68.4 y; 31% men; 41% white; baseline ECOG PS 0 = 48%, 1 = 31%, 2 = 21%) have been analyzed. 19 and 13 pts are evaluable at weeks 5 and 9, respectively. Prior CT and RT within 6 months were received by 21% and 31% of pts, respectively. The most common tumor types were prostate (38% of pts) and head and neck (24% of pts). Mean duration on study at preliminary analysis is 8 weeks. Hb increased from a mean baseline level of 10.5 g/dL ($n = 29$) by 2.2 ± 0.5 g/dL after 4 weeks of epoetin alfa therapy ($n = 19$), 2.9 ± 0.4 g/dL after 8 weeks ($n = 13$), and 3.1 ± 0.6 g/dL after 12 weeks ($n = 10$). Independent of transfusion, 13 (68%) pts had a Hb increase of ≥ 1 g/dL after 4 weeks of epoetin alfa therapy and 10 (77%) pts had a Hb increase of ≥ 2 g/dL after 8 weeks. Epoetin alfa dose was reduced to 30,000 U QW in 1 (3%) pt and escalated to 60,000 U QW in 4 (14%) pts. During the course of the study, 8 pts missed at least 1 dose of epoetin alfa: 1 pt at week 4, 3 pts at week 8, and 7 pts at week 12. Reasons for missed doses were Hb > 15 g/dL ($n = 6$), uncontrolled hypertension ($n = 1$), and nonadherence ($n = 1$). Mean LASA scores (mm) for Energy, Activity, and Overall QOL at baseline were 46.0 ($n = 28$), 52.2 ($n = 29$), and 51.9 ($n = 29$), respectively, and increased by 18.1 ($n = 11$), 3.3 ($n = 12$), and 16.1 ($n = 12$), respectively, after 8 weeks of therapy. These preliminary data suggest that epoetin alfa 40,000 U SC QW improves Hb and QOL in pts with cancer-related anemia not receiving CT or RT, as observed in pts with CT-related anemia. Updated data will be available at the meeting.

Abstract #4375 appears in Blood, Volume 102, issue 11, November 16, 2003

Abstract #4394 compares Eprex and Aranesp and determined that Eprex is more effective in stimulating the growth of erythroid bursts when low concentrations are used. It is not clear whether this difference may be of importance in vivo.

[4394] Comparison between Epoetin Alfa (E) and Darbeopetin Alfa (D) in the Stimulation of Human Erythroid Burst-Forming Units (BFU-E) In Vitro. Session Type: Publication Only

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Publication Only

Purpose: Both E and D are currently used in managing anemia in cancer patients, the effect of both growth factors on stimulation of human BFU-E has not yet been compared. Methods: Mononucleated hematopoietic progenitor cells obtained from bone marrow samples in three healthy subjects were cultured for 12 to 14 days using standard protocols in the presence of E or D at an amount ranging from 0.0083 to 16.7 ng. The number of BFU-E derived colonies was defined by:

$$\#BFU-E \text{ colonies} = \frac{E_{\max} C_{EPO}}{EC_{50} + C_{EPO}}$$

where E_{\max} and EC_{50} were the maximum effect (efficacy) and concentration resulting in 50% of the maximum effect (potency) respectively. C_{EPO} represents concentration of E or D. Darbeopetin alfa demonstrated no response for doses ≤ 0.167 ng. A threshold concentration C_{thresh} , below which darbeopetin alfa was not effective was used to modify E_{\max} for darbeopetin alfa as follows:

$$\#BFU-E \text{ colonies} = \frac{E_{\max} (C_{EPO} - C_{\text{thresh}})}{EC_{50} + C_{EPO} - C_{\text{thresh}}}, \text{ if } C_{EPO} \geq C_{\text{thresh}}$$

$$\#BFU-E \text{ colonies} = 0, \text{ if } C_{EPO} < C_{\text{thresh}}$$

The parameters E_{\max} , EC_{50} , and C_{thresh} were estimated from the individual, mean, and pooled data. The estimated values of EC_{50} for epoetin alfa and darbeopetin alfa were incorporated in an established PK/PD model to simulate hemoglobin responses of epoetin alfa and darbeopetin alfa in vivo.

Results: Detectable biological activity was observed for epoetin alfa at 0.0083 ng/mL compared to 1 ng/mL for darbeopetin alfa. The mean \pm SD of the estimated individual values were $E_{\max EPO} = 181.8 \pm 127.7$ and $E_{\max Darb} = 127.5 \pm 25.3$ of BFU-E derived colonies and $EC_{50 EPO} = 0.98 \pm 1.24$ and $EC_{50 Darb} = 8.28 \pm 5.38$ ng/mL. Epoetin alfa efficacy occurs at concentrations 8 fold lower than that of darbeopetin alfa. The quality of colonies from cultures with E were better than D. Therefore, despite the greater half-life of darbeopetin alfa, an 8 fold higher concentration is required to maintain a potency equivalent to that of epoetin alfa. Data from more marrow samples especially from cancer patients are being collected for comparison. Conclusions: E is more active and potent than D to promote erythroid burst formation in vitro.

Abstract #4394 appears in Blood, Volume 102, issue 11, November 16, 2003

Abstract #1811 is a randomized, open-label, multi-centre study designed to evaluate an early vs. late use of EPO in cancer patients. Early intervention appears to be of benefit in all areas tested.

[1811] Early Treatment with Epoetin Alfa Improves Anemia, Quality of Life (QOL), and Productivity in Patients (Pts) with Hematologic Malignancies and Mild Anemia during Chemotherapy (CT). Session Type: Poster Session 923-I

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ASH/ASCO guidelines recommend epoetin alfa treatment for cancer pts with hemoglobin (Hb) < 10 g/dL; for Hb 10-12 g/dL (mild anemia), epoetin alfa use should be determined by clinical circumstances. As clinical benefits of treating mild anemia are not well known, we conducted a randomized, open-label, multicenter trial comparing the effectiveness of epoetin alfa treatment (Hb response, QOL, health care resource utilization, and pt productivity) administered during CT to pts with mild anemia (Hb ≥ 10 g/dL and ≤ 12 g/dL; EARLY group) or after waiting until pts became moderately anemic (Hb < 9 g/dL; LATE group). Pts were enrolled if Hb ≥ 10 g/dL. Enrolled pts with Hb ≥ 10 g/dL and ≤ 12 g/dL were randomized either to the EARLY or LATE groups. Enrolled pts with Hb > 12 g/dL were randomized only if Hb decreased to ≤ 12 g/dL. Of 424 pts enrolled, 269 were randomized (EARLY, n=135; LATE, n=134). Epoetin alfa dosage was 40,000 U SC once weekly (QW) for 16 weeks, with dose escalation to 60,000 U QW permitted. Pts with non-Hodgkin's lymphoma (85%), Hodgkin's disease (5%), chronic lymphocytic leukemia (4%), or multiple myeloma (6%) were enrolled at start of first CT cycle. Baseline (BL) mean (\pm SE) Hb at randomization was 11.1 ± 0.7 g/dL (EARLY) vs 11.2 ± 0.7 g/dL (LATE). Both groups were well matched for gender, age, and performance status. Hb decreased to < 9 g/dL in 19.4% (n=26) of LATE pts: these pts received epoetin alfa for a median of 11 weeks. In the EARLY group, mean (\pm SE) Hb increased from BL during treatment by 1.2 ± 0.12 g/dL (P < 0.0001) (median 14 weeks of epoetin alfa treatment), compared with a mean decrease in Hb from BL of 0.2 ± 0.09 g/dL in the LATE group (P < 0.0001 between groups). Mean Hb increased for EARLY pts and remained stable for LATE pts during months 1, 2, 3, and 4 post randomization (12.1, 12.6, 12.7, 12.9 g/dL vs 11.0, 11.0, 10.8, 10.9 g/dL, respectively; P < 0.0001 between groups). At study end, 70.4% of EARLY pts and 25.4% of LATE pts (P < 0.0001) had a hematologic response (Hb ≥ 12 g/dL or increase ≥ 2 g/dL). More LATE pts (26.1%) required ≥ 1 RBC transfusion than EARLY pts (17.8%) (P=.11); average weekly transfusion rate was 75% higher (4.2% vs 2.4%) during post randomization months 2-4 (P < 0.05). Comparisons of BL-adjusted QOL scores between groups were significant for (+ values favor the EARLY group): Functional Assessment of Cancer Therapy (FACT)-General (G) physical well being, +1.2 (P=.007); FACT-G functional well being, +1.1 (P=.024); FACT-Anemia (An) Fatigue, +2.7 (P=.005), FACT-An Total, +3.2 (P=.008); Linear Analog Scale Assessment (LASA) Energy, +6.0 (P=.007); and LASA Activity, +6.0 (P=.008). Hb increases were significantly correlated with these QOL changes (P < 0.05). EARLY pts had significantly greater reductions than LATE pts in number of days spent in bed (52.2% vs 3.1%; P=.017) and restricted activity days (41.6% vs 12.2%; P=.042). There was also a trend toward reductions in nights in hospital, clinic visits, and calls to physicians in favor of EARLY pts. This study demonstrates advantages to treating mild anemia in pts on CT for hematologic malignancies, with significant increases in Hb, reduction in transfusion rates, and improvements in QOL and productivity compared with waiting until anemia becomes more severe (Hb ≤ 9 g/dL).

Abstract #1811 appears in Blood, Volume 102, issue 11, November 16, 2003

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New oral anticoagulants: Close but not here yet.

The advent of low-molecular heparins has revolutionized the treatment of patients with thromboembolic disorders. From hospitalization to total outpatient care, many patients benefit from these drugs. The only

drawback has been the need for parenteral administration, although often by the subcutaneous route. At ASH 2003 two new drugs were profiled: an oral direct thrombin inhibitor and an oral anti-Xa drug. Abstract #7 is an international randomized, double-blind, double-dummy trial with 2489 patients with acute deep vein thrombosis of whom 37% had confirmed pulmonary embolism. The patients were randomized to receive either oral ximelagatran 36 mg bid for 6 months or sc enoxaparin 1 mg/kg bid for a minimum of 5 days followed by warfarin (INR 2-3) for 6 months. Stringent scientific criteria were applied for care and monitoring. The demographics for both arms were comparable. The study was powered to show noninferiority of ximelagatran. Conclusion: During 6 months, treatment with oral ximelagatran in fixed dose and without coagulation monitoring, was non-inferior to standard therapy with enoxaparin/warfarin liver function abnormalities were found in 9.6% of ximelagatran treated patients vs. 2% for warfarin. Ximelagatran was also associated with a favourable outcome with respect to major bleeding.

[7] Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran Compared with Current Standard Therapy for Acute, Symptomatic Deep Vein Thrombosis, with or without Pulmonary Embolism: The THRIVE Treatment Study.

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Introduction: Current treatment of acute venous thromboembolism (VTE) consists of iv unfractionated heparin (UFH) or sc low-molecular-weight heparin (LMWH) followed by oral vitamin K antagonists (VKAs), such as warfarin. VKAs require coagulation monitoring and frequent dose adjustments due to a narrow therapeutic window and interactions with food and other drugs. Ximelagatran (Exanta, AstraZeneca), an oral direct thrombin inhibitor, has a rapid onset of action and its active form, melagatran, has predictable pharmacokinetics without known CYP450 drug or food interactions. Methods: In this international, randomized, double-blind, double-dummy trial, 2489 patients with acute deep vein thrombosis (DVT), of whom 37% had confirmed pulmonary embolism (PE), were randomly assigned to, and received, either oral ximelagatran 36 mg bid for 6 months, or sc enoxaparin 1 mg/kg bid for a minimum of 5 days followed by warfarin (target INR 2.0-3.0) for 6 months. An interactive, dose-responsive algorithm was used to produce shammed INR values in the ximelagatran arm. At baseline, bilateral compression ultrasonography of the legs and ventilation-perfusion lung scanning were performed. An independent committee adjudicated all recurrences of VTE, the primary endpoint, as well as bleeding events and mortality. The study aim was to determine whether ximelagatran is noninferior to enoxaparin/warfarin in the prevention of recurrent VTE, by comparing Kaplan-Meier estimates of the cumulative risk of an event at 6 months. Results: Ximelagatran was administered to 1240 patients and enoxaparin/warfarin to 1249 patients. The demographics of both groups were similar, with a mean age (\pm SD) of 57 \pm 16 years and 53% men. A comparison of the outcome of clinical endpoints between the 2 treatment groups, demonstrating noninferiority of ximelagatran versus enoxaparin/warfarin, is provided in the table.

Event	Ximelagatran, n (%)	Enoxaparin/warfarin, n (%)	Absolute difference ximelagatran - enoxaparin/warfarin, %* (95% CI)
Recurrent VTE (ITT)	26 (2.1)	24 (2.0)	+0.2** (-1.0; +1.3)
Recurrent VTE (OT)	23 (2.0)	17 (1.5)	+0.5 (-0.6; +1.6)
Major bleeding (OT)	14 (1.3)	26 (2.2)	-1.0 (-2.1; +0.1)
Recurrent VTE and/or major bleeding (OT)	37 (3.2)	43 (3.7)	-0.5 (-2.0; +1.0)
All-cause mortality (ITT)	28 (2.3)	42 (3.4)	-1.1 (-2.4; +0.2)
All-cause mortality (OT)	7 (0.7)	10 (0.9)	-0.2 (-1.0; +0.5)

*Estimated cumulative risk; **rounded figure; CI = confidence interval; ITT = intention-to-treat; OT = on-treatment

Laboratory evaluation showed an incidence of serum alanine aminotransferase (ALAT) elevations (> 3 times the upper limit of normal) of 9.6% for patients receiving ximelagatran versus 2.0% for patients receiving enoxaparin/warfarin. Conclusion: During 6 months of treatment, oral ximelagatran, administered in fixed doses of 36 mg bid without coagulation monitoring, was noninferior to enoxaparin/warfarin in preventing recurrent VTE in patients with acute DVT with or without PE. Ximelagatran was associated with a favorable outcome with respect to major bleeding.

Abstract #7 appears in Blood, Volume 102, issue 11, November 16, 2003

Also an international study, Abstract #41, in patients undergoing elective knee replacement was presented. Patients were randomized into a double-blind, controlled design to 4 doses of Razaxaban: 25 mg, 50 mg, 75 or 100 mg given twice daily and started 8 hours after the end of surgery or into the LMWH, enoxaparin 30 mg twice daily 12-24 after surgery and continued for 10-12 days with a mandatory bilateral venography at the end of study period, and all were assessed at 42 days. Of 656 patients, 438 were eligible for efficacy analysis. An 8.6% (95% CI) VTE was observed with Razaxaban 25 mg bid compared to 15.9% (95% CI) with enoxaparin. There was increased bleeding for the 3 larger doses of Razaxaban and these dose studies were stopped before the intended sample size of 150 patients. Bleeding was mainly at the operative site. At the 25 mg bid dose the incidence of major bleeding was 0.7% with Razaxaban vs. 0% (95% CI) with enoxaparin. The authors conclude that the oral-acting factor Xa inhibitor Razaxaban at 25 mg bid, appears attractive for preventing venous thromboembolism after major orthopedic surgery, with increased efficacy and similar safety to standard dose enoxaparin. Two exciting studies that show the future, if the efficacy and safety trends continue to be demonstrated and pricing is affordable.

[41] A Phase II Randomized, Double-Blind, Five-Arm, Parallel-Group, Dose-Response Study of a New Oral Directly-Acting Factor Xa Inhibitor, Razaxaban, for the Prevention of Deep Vein Thrombosis in Knee Replacement Surgery - on Behalf of the Razaxaban Investigators. Session Type: Oral Session

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Background: Major joint replacement is still complicated by venous thromboembolism calling for new antithrombotic drugs and more effective and safe regimens. Razaxaban is a new orally active and directly acting inhibitor of coagulation factor Xa. Razaxaban binds to the active site of factor Xa without requiring anti-thrombin III. To investigate this new antithrombotic agent, we performed a dose-ranging study.

Methods: Patients undergoing elective primary total knee replacement were allocated randomly in a double-blind controlled design to 4 doses of Razaxaban: 25 mg, 50 mg, 75 mg, or 100 mg given twice-daily and started 8 hours after the end of surgery or to a low molecular weight heparin, enoxaparin, 30 mg twice-daily given subcutaneously and started 12-24 hours after the end of surgery. Treatment was continued for 10±2 days and a mandatory bilateral venography was performed at the end of treatment. Patients could continue on extended, non-study drug prophylaxis according to the attending physician's discretion. All patients were seen at follow-up on day 42. The primary efficacy outcome measure was defined as a composite of asymptomatic deep vein thrombosis (DVT), symptomatic DVT and pulmonary embolism (PE) during the treatment period. A central independent committee whose members were unaware of treatment assignments adjudicated all DVTs and PEs as well as all bleeding, thrombocytopenia and death.

Results: Of 656 subjects treated and included in the safety analysis, 438 were eligible for the efficacy analysis. The clear relationship identified between razaxaban dose and rates of venous thromboembolism (VTE) is shown in the table (point estimates and 95% confidence intervals). An 8.6% (95% CI: 3.8 to 16.2%) VTE rate was observed with razaxaban 25mg BID compared to a 15.9% (95% CI: 9.5 to 24.2%) VTE rate with enoxaparin. The safety analysis (major bleeding) also showed a dose dependent effect (see table). A 0.7% (95% CI: 0.0-3.7%) major bleeding incidence was observed with razaxaban 25mg BID compared to a 0% (95% CI: 0.0 to 2.4%) incidence with enoxaparin. The 3 highest doses were stopped before the intended per-group sample size of 150 patients was reached due to increased reports of bleeding, mainly at the surgical site.

Conclusions: The oral directly-acting factor Xa inhibitor razaxaban, at 25 mg bid, appears attractive for preventing venous thromboembolism after major orthopedic surgery, with increased efficacy and similar safety to enoxaparin at 30 mg bid.

NOTE: Venous thromboembolic event; DVT: Deep venous thrombosis; PE: Pulmonary embolism.

Efficacy and major bleeding with 95% confidence interval

Event	Razaxaban 25 mg bid (N=147)	Razaxaban 50 mg bid (N=123)	Razaxaban 75 mg bid (N=115)	Razaxaban 100 mg bid (N=121)	Enoxaparin 30 mg bid (N=150)
Patients with efficacy end-point	93	84	83	71	107
VTE % (95% C.I.)	8.6 (3.8-16.2)	6.0 (2.0-13.3)	3.6 (0.8-10.2)	1.4 (0.0-7.6)	15.9 (9.5-24.2)
Proximal DVT or PE % (95% C.I.)	2.2 (0.3-7.6)	2.4 (0.3-8.3)	2.4 (0.3-8.4)	0.0 (0.0-5.1)	6.5 (2.7-13.0)
Major bleeding % (95% C.I.)	0.7 (0.0-3.7)	4.1 (1.3-9.2)	3.5 (1.0-8.7)	5.8 (2.4-11.6)	0.0 (0.0-2.4)

VTE: Venous thromboembolic event; DVT: Deep venous thrombosis; PE: Pulmonary embolism.

Abstract #41 appears in Blood, Volume 102, issue 11, November 16, 2003

New prognostic marker with potential therapeutic role in the treatment of Acute Myeloid Leukemia (AML).

Despite significant improvement in the therapeutical options and supportive measures available to patients diagnosed with AML, the long term outcome of older patients (> 60 years), which constitutes the bulk of the population diagnosed with the disease have not changed over the last 10-20 years with a dismal 5 years survival rate of approximately 10%. It is well recognized that older patients frequently present with poor prognostic features (unfavourable cytogenetics, poor performance status etc.) and other co-morbid conditions (cardiovascular disease, diabetes, etc.) making them less tolerant to standard chemotherapy treatment. Dr. James D. Griffin reviewed the potential role of tyrosine kinases in the pathogenesis of AML and as therapeutic targets presented a review on the topic at the educational session. Several abstracts were presented on the same topics at the simultaneous and the poster sessions. They include Abstracts # 219, 220 and 221 for treatment options, and Abstracts # 335, 336 for prognosis. Tyrosine kinases are enzymes that phosphorylate proteins on tyrosine residues and function in signal transduction cascades. These signals mediate a variety of cellular activities including differentiation, growth and cell death. The majority of known mutations in tyrosine kinases in AML are members of the Class III receptor tyrosine kinase family, one of the most interesting being FLT3. FLT3 is mutated in approximately 30% of patients with AML making it the single most common genetic abnormality in the disease. The most common type of mutation consists of internal tandem duplications of amino acids (ITD). AML with FLT3-ITDs are associated with a significantly greater risk of relapse and reduced survival according to several retrospective studies. There has been significant interest in developing FLT3 inhibitors because of the high incidence and poor prognosis of AML patients with mutant FLT3. Four (4) compounds: (CEP-701, Cephalon, Inc., West Chester, PA; CT53518 (MLN518); PKC412, Novartis Pharmaceuticals, Basel, Switzerland; SU5416, SU5614 and SU11248, Sugen, San Francisco, Ca.) are currently under development, with ongoing phase I and II studies demonstrating a good oral tolerability and some clinical response (decrease in peripheral blasts counts in some patients). These promising results confirm the great potential of FLT3 inhibitors as molecular target for therapy of AML and open the way to targeted treatment in that disease.

A Canadian study helping set the state-of-the-art treatment of early stage Hodgkin's disease.

The treatment of Hodgkins lymphoma is among the great successes of modern medicine, with improved treatment outcomes demonstrated over the last 5 decades, as elegantly reviewed by Prof. Volker Diehl for the German Hodgkin Lymphoma Study Group at the ASH meeting. With treatment leading to results as high as approximately 90% 5 year's disease-free-survival (DFS) in early stage, the treatment goal is now targeting reduced secondary effects, improved early and long term toxicity, while preserving the high response rate, DFS and survival. The standard treatment for early stage favourable disease (Stage I and II without risk factors) have changed from extended field radiotherapy alone to combined modality treatment using 2-4 cycles of chemotherapy followed by involved field irradiation. Risk factors for early stage disease (Stage I and II) may slightly differ from study to study or in between continent but globally include a large mediastinal mass or bulky disease (nodal mass >10 cm), elevated ESR, extra-nodal disease, B symptoms and ≥ 3 involved regions). The short course of chemotherapy aims to control occult disease, while the involved field irradiation aims to reduce the long-term effect of irradiation. One unsolved question is the role of chemotherapy alone in the treatment of early stage favourable disease. Many ongoing trials are looking at that question. Dr. Ralph Meyer, Abstract #81, reported at the meeting the results of a first analysis of the HD-6 trial of the NCIC and ECOG trial JHD06, a Randomized phase III comparison of single modality ABVD with a strategy that includes radiation therapy in patients with early-stage Hodgkins Disease. (Abstract 81) This first interim analysis evaluates 5-year progression-free survival (PFS), event-free survival (EFS) and overall survival (OS). In the study, patients were stratified into low and high-risk categories. Low risk patients received standard therapy consisting of subtotal nodal irradiation (STNI) while high-risk patients received combined modality ABVD x 2 cycles followed by STNI. All patients randomized to the experimental arm received single-modality ABVD x 4 cycles. PFS is inferior in patients randomized to chemotherapy alone with a trend toward inferior EFS while there is still no difference in overall survival between both groups. Interestingly, the unfavourable group of patients is doing

better on combined modality treatment. The authors conclude that in early stage HD, combined modality treatment is associated with superior 5 year PFS in comparison to chemotherapy alone helping further defining the state-of-the-art treatment of early stage Hodgkins disease.

[81] A Randomized Phase III Comparison of Single - Modality ABVD with a Strategy that Includes Radiation Therapy in Patients with Early-Stage Hodgkin's Disease: The HD-6 Trial of the National Cancer Institute of Canada Clinical Trials Group (Eastern Cooperative Oncology Group Trial JHD06). Session Type: Oral Session

Ralph Meyer, Mary Gospodarowicz, Joseph Connors, Robert Pearcey, Andrea Bezjak, Woodrow Wells, Bruce Burns, Jane Winter, Sandra Horning, Rashid Dar, Marina Djurfeld, Lois Shepherd, Keyue Ding Hematology, Hamilton Regional Cancer Centre and McMaster University, Hamilton, ON, Canada; Radiation Oncology, Princess Margaret Hospital, Toronto, ON, Canada; Medical Oncology, British Columbia Cancer Agency, Vancouver, BC, Canada; Radiation Oncology, Cross Cancer Institute, Edmonton, AB, Canada; Pathology, Ottawa Hospital, Ottawa, ON, Canada; Hematology / Oncology, Northwestern University, Chicago, IL, USA; Medical Oncology, Stanford University Medical Center, Palo Alto, CA, USA; Radiation Oncology, London Regional Cancer Centre, London, ON, Canada; National Cancer Institute of Canada Clinical Trials Group, Queens University, Kingston, ON, Canada

The long-term survival of patients with early-stage Hodgkin's disease (HD) is determined by the control of HD and the occurrence of treatment-related toxicities. Long-term treatment-related toxicities (late-effects) include an increased incidence of second malignancies and cardiovascular events and have been attributed to radiation therapy (RT). We hypothesized that treatment with single-modality ABVD would reduce the incidence of late-effects and improve long-term survival. The primary objective of this randomized phase III trial is to compare the 12-yr overall survival (OS) of patients with early-stage HD treated with ABVD with those receiving standard therapy that includes RT. Secondary outcomes include 5 and 10-yr progression-free (PFS) and event-free (EFS) survivals, quality of life, response and toxicity. We now report the results of a first analysis evaluating 5-yr PFS, EFS and OS. Eligible patients had non-bulky clinical stage I-IIA HD; patients with sub-diaphragmatic disease were eligible provided disease was confined to the iliac, inguinal and/or femoral regions. Prior to randomization, patients were stratified into low and high-risk categories. Low-risk patients had all of lymphocyte predominant or nodular sclerosis histology, age < 40 yrs, ESR < 50, and involvement of 3 or fewer disease-site regions; all others were categorized as high-risk. Patients randomized to standard therapy received single-modality subtotal nodal irradiation (STNI) if categorized as low-risk and combined-modality ABVD (2 cycles) plus STNI if categorized as high-risk. All patients randomized to the experimental arm received single-modality ABVD (4 cycles); those not demonstrating a complete remission with restaging performed after 2 cycles received 6 cycles. Between March 1994 and April 2002, 405 patients were entered; 399 were eligible and are included in this intent-to-treat analysis. The median duration of follow-up is 4.2 years. In comparison with patients randomized to standard therapy, PFS was inferior in patients randomized to ABVD (P = .006; HR = 2.6; 5-yr estimates 87% vs. 93%) and there was a trend toward inferior EFS (P = .06; HR = 1.7; 5-yr estimates 86% vs. 88%). No difference in OS has been detected (P = .42; HR = .7) with 5-yr estimates of 96% (ABVD) and 94% (standard therapy). Causes of death in standard arm patients (n = 9) include HD (1), second cancers (4), respiratory toxicity (2), cardiovascular disease (1) and drowning (1). Causes of death in experimental arm patients (n = 6) include HD (2), second cancers (2), respiratory toxicity (1), and cardiovascular disease (1). We conclude that in patients with early-stage HD, treatment that includes RT is associated with superior 5-yr PFS in comparison with single-modality ABVD. To date, no difference in OS has been detected. Further follow-up is required to determine whether treatment with single-modality ABVD is associated with improved long-term survival through a reduced incidence of late-effects.

Abstract #81 appears in Blood, Volume 102, issue 11, November 16, 2003

Impact of low-dose aspirin on reducing the thrombotic risk in patients with Polycythemia Vera.

Despite effective treatment in polycythemia vera (PV), the course of the disease is still complicated by significant risk of thrombotic events, contributing to its morbidity and mortality. While elevated red blood cell mass with associated increased blood viscosity is a risk factor for thrombosis in untreated patients, the continued high risk of thrombotic events despite a good control of the hematocrit lead to the investigation of possible mechanisms of thrombogenesis in the disease. One of the interesting findings is the consistently increased in vivo thromboxane production detected in PV patients making the use of aspirin (ASA) appealing in the disease to prevent thromboxane formation and to reduce the thrombotic risk. A first study, looking at the role of aspirin in PV was done and published in 1986 by the Polycythemia Vera Study Group (PVSG 05 trial), but prematurely closed because of an excess of hemorrhagic events in the treated arm reducing significantly the enthusiasm surrounding anti-platelets therapy in preventing thrombotic complications in the disease. The dose of aspirin used was quite high (900mg/day) contributing to the excessive bleeding. Drs Roberto Marchioli and Gianni Tognoni, Abstract #5, reported at the last December ASH meeting, the first preliminary results of the European Collaboration on Low-dose aspirin In Polycythemia Vera (ECLAP) Project. At the time of randomization, patients were being treated for the disease with a median hematocrit value of 0.46, a median platelet count of $321 \times 10^9/L$. Patients with no clear indication or contraindication for aspirin treatment were randomized in a double-blind, placebo-controlled study comparing daily low-dose aspirin (100mg) to no treatment. The trial demonstrates that treatment with aspirin reduced the risk of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis or death from cardiovascular causes while the incidence of major bleeding episodes was not significantly increased in the ASA group. The authors concluded that low-dose ASA can safely prevent thrombotic complications in patients with PV who have no contraindications to such treatment. This study underlines the importance of collaborative efforts in the management of rare disease and demonstrates that low cost therapeutic intervention can have significant impact on the morbidity and mortality of a disease and possibly increase the quality of life of patients living with Polycythemia Vera.

[5] Efficacy and Safety of Low-Dose Aspirin In Polycythemia Vera (ECLAP Study).

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The thrombotic diathesis affecting patients with Polycythemia Vera (PV) is generally treated by cytoreduction while benefit and safety of aspirin administration are unknown. This together with the finding of an aspirin suppressible *in vivo* thromboxane hyperproduction in polycythemic subjects suggested to test the effect of low-dose aspirin (100 mg daily) in PV.

The ECLAP study is a multi-country, multi-centre, parallel, double-blind, randomised clinical trial. Overall, 1630 PV patients from 12 Countries (Austria, France, Germany, Greece, Ireland, Israel, Italy, Spain, Sweden, Switzerland, The Netherlands, and the United Kingdom) were included in the ECLAP project. About one third (n=518) of these patients were judged by the responsible physician to have no clear indication for- or contraindication to- aspirin treatment and were randomly allocated aspirin (100 mg daily) or placebo (males 60%, mean age 61 years, mean disease duration 7 years, prior thrombotic event 13%). The main reasons for excluding the patients from the trial were: need of antithrombotic therapy (66%), contraindication to ASA (23%), patients unwillingness (18%) The study was independently conceived, conducted, and analysed by the ECLAP investigators and was partially funded by the European Union (BIOMED 2 Program, contract no. ERBBMH4CT961433) and by an unrestricted grant from BAYER A.G. The follow-up duration was about three years. Treatment with aspirin was found to lower the risk of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (relative risk 0.41 [95% CI 0.15-1.16], P = 0.0920) and of all major arterial and venous thromboses which constituted the other primary end-point of the study (relative risk 0.40 [95% CI 0.18-0.90], P=0.0274). The probability of major thromboses of placebo and aspirin treated subjects is reported in the figure. The risk of both major and minor thrombotic events was also significantly decreased (relative risk 0.43 [95% CI 0.25-0.76], P=0.0039). Total and cardiovascular mortality were reduced, though not significantly, by 46% and 59%, respectively. Major, total, and gastrointestinal bleedings were slightly, but not significantly increased (relative risk 1.08, 1.70, and 3.14, respectively). Only the risk of epistaxis was significantly increased (relative risk 9.43 [95% CI 1.20-73.90], P=0.0327). In conclusion aspirin administration (100 mg daily) significantly reduced the risk of thrombosis in polycythemic patients under standard cytoreductive treatment. No excess of major bleedings was observed in patients allocated aspirin treatment. These results indicating a high benefit/risk ratio of aspirin in a low risk polycythemic population, suggest that aspirin should be used in all polycythemic subjects having no contraindication to this treatment.

Abstract #5 appears in Blood, Volume 102, issue 11, November 16, 2003



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*The publication of this booklet was supported
by an unrestricted grant from
Ortho Biotech.*