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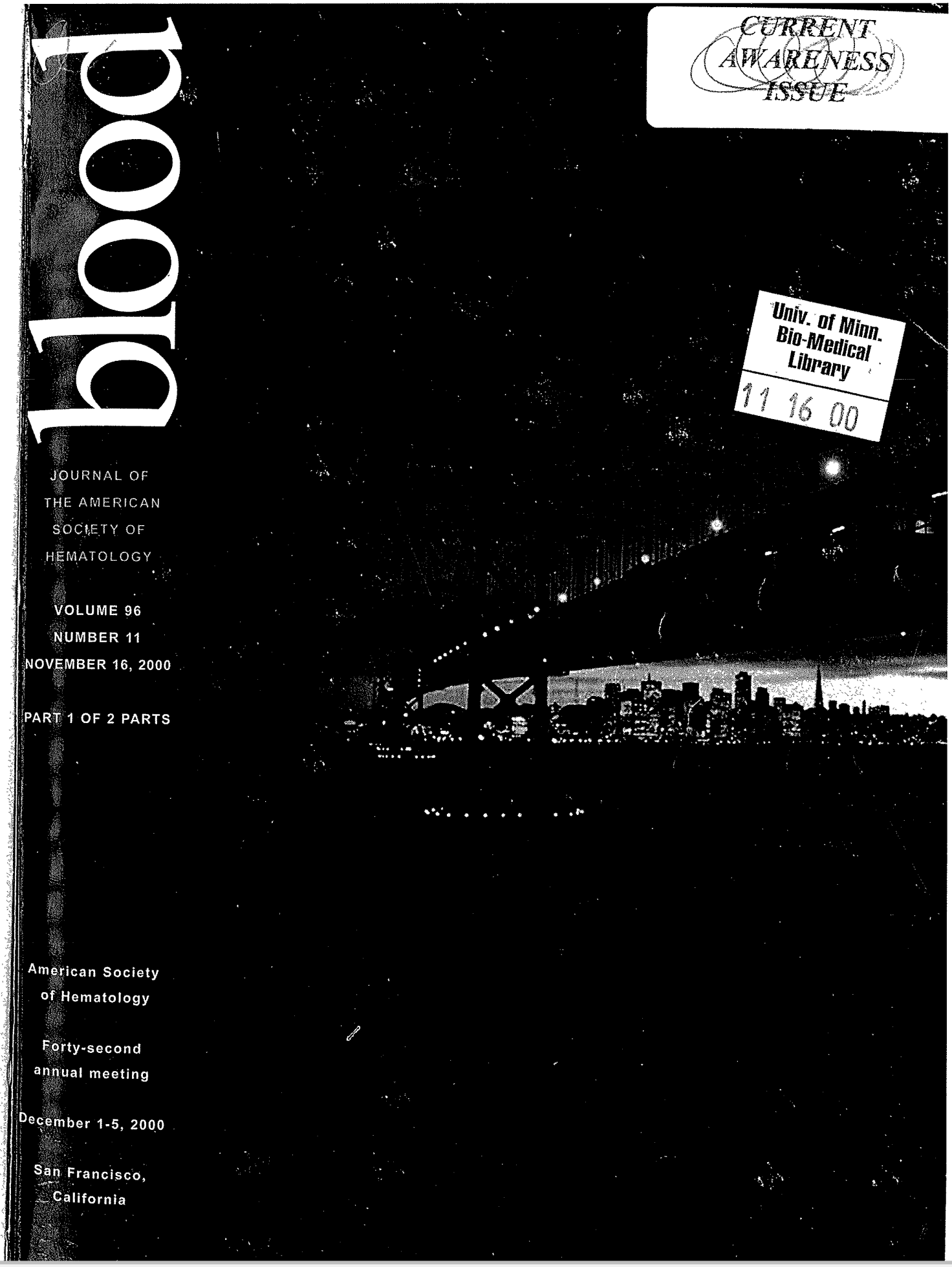

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Abstract# 722 **Poster Board #-Session: 722-I**

THALIDOMIDE PLUS DEXAMETHASONE (THAL/DEX) AND THALIDOMIDE ALONE (THAL) AS FIRST LINE THERAPY FOR NEWLY DIAGNOSED MYELOMA (MM). S.V. Rajkumar,[1] S. Hayman,[1] R. Fonseca,[1] A. Dispenzieri,[1] M.Q. Lacy,[1] S. Geyer*,[1] L. Wellik*,[1] J.A. Lust,[1] R.A. Kyle,[1] P.R. Greipp,[1] M.A. Gertz,[1] T.E. Witzig.[1] [1]*Hematology, Mayo Clinic, Rochester, MN, USA.*

Background: A phase II trial of Thal/Dex combination and Thal as first line therapy in new untreated MM with laboratory correlative studies (interim analysis).

Methods: Patients (pts) with active MM were treated with the Thal/Dex combination. Pts with smoldering or indolent MM (SMM/IMM) were treated with Thal alone Thal was given orally at a dose of 200 mg/day for 2 weeks, and then increased as tolerated by 200 mg/day every 2 weeks to a maximum dose of 800 mg/day. Dex was given orally at a dose of 40 mg/day orally on days 1-4, 9-12, 17-20 (odd cycles) and 40 mg/day days 1-4 (even cycles) repeated monthly. Response was defined as a decrease in serum and urine monoclonal (M) protein by 50% or greater. Bone marrow (BM) microvessel density (MVD) using immunostaining for CD34 was estimated by determining the average number of vessels in 3 hot spots at 400x magnification. BM angiogenesis was also visually graded as low, intermediate and high.

Results: 42 pts (26 with active MM and 16 with smoldering/indolent MM) were studied In the Thal/Dex arm, 2 pts had grade 3-4 skin toxicity among the first 7 pts treated, at Thal dose of 400mg. The Thal/Dex arm was then amended to stop dose escalation, and keep Thal dose constant at 200mg. An objective response was seen in 20 pts (77%) with active MM treated with Thal/Dex. The response rate was 86% with Thal dose escalation (6 of 7 pts), and 74% with Thal dose constant at 200mg (14 of 19 pts). Major grade 3-4 toxicities were rash in 3 pts, and sedation, constipation and myalgias in 1 pt each. In the SMM/IMM arm, 6 pts (38%) achieved a response with Thal alone Median pre-treatment MVD was 27 in the active MM arm, and 7 in the SMM/IMM arm ($p<0.001$). Angiogenesis grade was high in 64% of active MM and 8% of SMM/IMM, ($p<0.001$) The proportion of pts with a high(>1) PCLI was 67%, 9%, 0% for high, intermediate, and low grade angiogenesis respectively ($p<0.001$). No significant changes were observed in MVD following treatment; pre-treatment MVD and angiogenesis grade did not appear to be associated with response to therapy.

Conclusions: Thal/Dex is strikingly effective as first line therapy (and an oral alternative to infusional VAD) for new, active MM. SMM/IMM pts also appear to achieve significant responses with Thal alone. However, these results are preliminary and responses/toxicities are still being evaluated and need further confirmation in the final analysis of this trial.

Abstract# 723 **Poster Board #-Session: 723-I**

A PHASE II TRIAL OF THALIDOMIDE IN THE TREATMENT OF RELAPSED MULTIPLE MYELOMA (MM) WITH LABORATORY CORRELATIVE STUDIES. S.V. Rajkumar,[1] R. Fonseca,[1] A. Dispenzieri,[1] M.Q. Lacy,[1] S. Geyer*,[1] L. Wellik*,[1] S. Hayman,[1] J.A. Lust,[1] R.A. Kyle,[1] P.R. Greipp,[1] M.A. Gertz,[1] T.E. Witzig.[1] [1]*Hematology, Mayo Clinic, Rochester, MN, USA.*

Aim: A phase II trial of thalidomide in relapsed MM with laboratory correlative studies examining bone marrow (BM) angiogenesis and plasma cell proliferation.

Methods: 32 patients (pts), 22 male and 10 female, with relapsed MM were treated between April 1999 and July 2000. Thalidomide was given orally at a dose of 200 mg/day for 2 weeks, then increased as tolerated by 200 mg/day every 2 weeks, up to a maximum daily dose of 800 mg/day. Response was defined as a decrease in serum and urine monoclonal (M) protein by 50% or greater, and confirmed by repeat measurements at least 2 weeks apart. BM angiogenesis was studied in a blinded manner using immunohistochemical staining for CD34 to identify microvessels in 27 pts (84%). Microvessel density (MVD) was estimated by determining the average number of vessels in 3 hot spots examined at 400x magnification. Angiogenesis was also visually graded as low, intermediate and high Plasma cell (PC) proliferation was studied using a slide based immunofluorescent bromodeoxyuridine incorporation assay (plasma cell labeling index, PCLI).

Results: The median age was 67 years (range, 36-78) All pts had failed prior chemotherapy and 5 (16%) had failed stem cell transplantation. Response is still being evaluated, and currently 26 patients with at least two cycles of data are evaluable for response. 10 responses were confirmed, yielding a response rate of 38%. No complete responses were seen. Major grade 3 toxicities were sedation (10%) and neuropathy (10%). One pt each had grade 3 constipation, rash and vertigo. Pre-treatment MVD ranged 5-47 per 400x field (median 20) Angiogenesis grade was high in 52%, intermediate in 30%, and low in 18% No significant changes were observed in MVD following treatment in 4 responders on whom at least 2 BM samples were available for study Pre-treatment MVD and angiogenesis grade did not appear to be associated with response to therapy Response rates were significantly higher in pts with a high PCLI (≥1) compared to those with a low PCLI, 57% versus 21%, respectively, ($p=0.02$)

Conclusions: Thalidomide is effective in the treatment of relapsed MM with a response rate of 38% in this study. Its mechanism of action remains unclear. These results suggest that a high PCLI is a potential predictor of response to therapy.

Abstract# 724 **Poster Board #-Session: 724-I**

ANGIOGENESIS FACTORS AND SENSITIVITY TO THALIDOMIDE IN PREVIOUSLY UNTREATED MULTIPLE MYELOMA (MM). D.M. Weber, K. Rankin*, M. Gavino*, K. Delasalle*, A. Aguayo*, M. Albitar, R Alexanian *University of Texas M.D. Anderson Cancer Center, Houston, TX.*

Between 5/99 - 1/00 plasma levels of multiple angiogenesis factors (VEGF, bFGF, HGF, TNF-a, angiogenin) and cytokines (IL-6, IL-8, EGF, IL-1b) were assessed in 19 previously untreated patients with asymptomatic MM. The median level of VEGF (100 8 pg/mL) was 3.8 times higher than that of 11 control pts. with solid tumors (26.7 pg/mL) ($p< 05$), and higher than prior median levels measured for all categories of leukemic disorders Values of bFGF, HGF, and angiogenin were approximately double that of controls and similar to those observed previously in leukemia. Only minimal elevation of cytokines was noted. Marrow microvascular density was increased (median 14.5 blood vessels/ field) in 8 untreated pts with available samples compared to control pts. Because of the postulated antiangiogenic effect of thalidomide, an agent effective in resistant myeloma, we treated 26 previously untreated asymptomatic pts. with thalidomide in doses of 200 mg p o q. h s. increasing to a maximum of 600 mg. Partial response, defined by > 50% reduction of serum myeloma protein and/or > 75% reduction of Bence Jones protein, was achieved in 9 pts. (35%). Onset of response was rapid (median 1.5 months), and the projected mean remission duration was 14 months. Median VEGF of responding patients was 4 times that of nonresponding pts. (p.06); response was observed in 1 of 10 pts with VEGF < 100, and in 3 of 8 pts with VEGF > 100 (p.16). Microvascular density was available in only one responding pt., and the level of 23 vessels/field was the highest noted among 8 available specimens. Subsequent remissions occurred with high dose dexamethasone in 2 of 5 pts. with disease resistant to thalidomide. These observations justify further correlations of angiogenesis markers with thalidomide trials, extend the antimyeloma spectrum of thalidomide to previously untreated disease, and support further trials in combination with other active agents.

Abstract# 725 **Poster Board #-Session: 725-I**

HYPERFRACTIONATED CYCLOPHOSPHAMIDE IN COMBINATION WITH PULSED DEXAMETHASONE AND THALIDOMIDE (HYPER-CDT) IN PRIMARY REFRACTORY OR RELAPSED MULTIPLE MYELOMA. Martin H. Kropff*,[1] Georg Innig*,[2] Manfred Mitterer*,[3] Christian Straka*,[4] Helmut Ostermann,[5] Olaf M. Koch,[2] Wolfgang E. Berdel,[1] Joachim Kienast.[1] [1]*Department of Internal Medicine, Hematology/Oncology, University of Muenster, Muenster, Germany;* [2]*Department of Internal Medicine, Paracelsusklinik, Osnabrueck, Germany;* [3]*Abteilung für Hämatologie und KMT, Regionalkrankenhaus, Bozen, Italy;* [4]*Medical Clinic, Klinikum Innenstadt of Ludwig-Maximilians-University, Munich, Germany;* [5]*Medical Clinic III, Klinikum Großhadern, Munich, Germany.*

Thalidomide is active in ≈ 30 % of patients with advanced multiple myeloma (MM) Moreover, thalidomide has been reported to restore the sensitivity of myeloma cells to dexamethasone (DEX) The present phase II trial was intitiated to study the combination of thalidomide with pulsed DEX and hyperfractionated cyclophosphamide (HyperC). HyperC administered at the schedule employed in this study and combined with VAD has previously been shown to induce 40 % responses in VAD-resistant MM. 20 patients with advanced MM were treated with 2 to 6 monthly courses of HyperC (300 mg/m IV over 3 h q 12 h x 6 doses, days 1 - 3, total dose 1800 mg/m²) combined with pulsed DEX (20 mg/m²/d PO, days 1 - 4, 9 - 12, 17 - 20) and once daily thalidomide at individually escalating doses (100 to 400 mg/d) Supportive care included G-CSF, ciprofloxacin and non-absorbable antifungal agents. Responding patients were maintained on daily thalidomide and monthly DEX pulses. 6 patients had primary refractory disease on VAD or ID. 14 patients had relapsed after high-dose melphalan Patient characteristics included median age 63 years, B2M > 2,5 mg/L, 25 %; CRP > 4,0 mg/L, 10 %; and prior standard therapy > 12 mo, 80 % Among 14 evaluable patients, 12 (86 %) achieved a partial remission (PR); as yet, no complete remission. After a median follow-up of 7 months (2 - 14), all 12 PR patients are alive and free of disease progression. 10/20 patients experienced grade 4 neutropenia during at least one cycle; no grade 4 thrombocytopenia. There were two grade 3/4 infections. one patient died during neutropenic pneumonia; another patient developed neutropenic colitis but recovered Other side effects included grade 2 constipation (35 %), grade 2/3 skin reactions (15 %), and 1 deep venous thrombosis. In 3 patients thalidomide was stopped due to neurotoxicity (2) or skin reaction (1), and treatment was continued with HyperCD. In addition, 5 patients required a dose limitation of thalidomide to 300 mg (1), 200 mg (1), or 100 mg (3) due to neurotoxicity. HyperCDT appears to be a highly active and teasonably well tolerated regimen in advanced MM

Abstract# 726 **Poster Board #-Session: 726-I**

DURABLE RESPONSE TO THALIDOMIDE IN RELAPSED/ REFRACTORY MULTIPLE MYELOMA (MM). Syed N. Raza*,[1] Yuliya Veksler*,[1] Tariq Sabir*,[1] Zujun Li*,[1] Lorraine Anderson*,[1] Sundar Jagannath.[1] [1]*St. Vincents Comprehensive Cancer Center, New York Medical College, New York, NY, USA.*

Recently Thalidomide has re-emerged as a promising anti-cancer agent in many refractory malignancies due to its inhibitory effects on angiogenesis (via b-FGF) and on TNF-α Last year we reported the impressive efficacy of Thalidomide in relapsed/refractory MM An update with more patients (pts) and longer follow-up (F/U) is presented here We have treated 35 pts with relapsed/refractory MM from March 1998 to July 2000, with a median F/U of 12 months (mo) (range 6-28+) Median age was 58yrs (range 33-77). Median number of prior chemotherapies was 3 (range 1-8). 12 pts had one and 3 pts had