SATELLITE SYMPOSIA

SATELLITE SYMPOSIUM

LONG-TERM RESULTS & CLINICAL PROGRESS IN LYMPHOMA THERAPY

Tuesday, June 8, 1993

Room A - 1:30-5:30 p.m.

A Randomized Comparative Study of CHOP and CNOP Regimens in the Treatment of Intermediate- and High-Grade Lymphoma With 8 Years' Follow-up

Werner R. Bezwoda, MB BCh, FCP(SA), PhD*

A randomized, multicenter, Phase III trial was conducted to compare the efficacy and safety of the CHOP and CNOP regimens in patients with intermediate- and high-grade, stage II to IV, non-Hodgkin's lymphoma (NHL). The CHOP regimen consisted of cyclophosphamide 750 mg/m², vincristine 1.4 mg/m², and doxorubicin 50 mg/m² on Day 1, and prednisone 50 mg/m² on Days 1 to 5. The CNOP regimen was identical to CHOP, except that mitoxantrone 10 mg/m² was substituted for doxorubicin. A total of 359 patients were accrued; 325 were appropriately randomized and were included in the efficacy and survival analyses. The two treatment groups were well-balanced with respect to patient age, sex, and performance status. However, there were imbalances in the distribution of patients based on stage and histologic grade of disease. There were more patients with stage II disease in the CNOP group than in the CHOP group, and there were more patients with stage III disease in the CHOP group than in the CNOP group. Furthermore, there were slightly more patients with intermediate-grade disease in the CHOP group than in the CNOP group and slightly more patients with high-grade NHL in the CNOP group than in the CHOP group.

Eighty-three of the 164 patients (51%) randomized to the CHOP regimen achieved complete remissions (CR) compared with 64 of 161 patients (40%) randomized to receive CNOP ($P = 0.049$). An additional 23 patients in the CHOP group and 32 patients in the CNOP group achieved partial remissions, resulting in overall response rates of 65% and 60%, respectively ($P = 0.35$). The median duration of CR was 667 days in patients receiving the CHOP regimen compared with 1,833 days in those receiving the CNOP regimen. The median survival was 932 days (range, 0–2,890 days) for CHOP and 1,801 days (range, 0–2,959 days) for CNOP-treated patients ($P = 0.62$; hazard ratio, 0.93). The median duration of follow-up was 450 days (range, 0–2,682 days) for patients in the CHOP group and 490 days (range, 0–2,813 days) for patients in the CNOP group. At the end of 5 years, 50% of patients treated with CNOP and 40% of patients treated with CHOP were still alive. The most common cause of death was disease progression.

The number of patients experiencing at least one adverse experience, regardless of severity, was similar in the two treatment groups. However, a significantly higher number of patients receiving CHOP ($P \leq 0.008$) experienced severe nausea and vomiting, alopecia, and mucositis compared with those receiving CNOP. Severe neutropenia occurred in 40% of the CNOP courses compared with 26% of the CHOP courses. However, the different incidences of neutropenia did not appear to have any clinical impact since the incidence and the severity of infection were similar in the two treatment groups. It was concluded that both the CNOP and CHOP regimens are effective in previously untreated patients with intermediate- and high-grade NHL. Furthermore, severe nausea and vomiting, alopecia, and mucositis occurred less frequently in CNOP-treated patients than in CHOP-treated patients.

Comparison of Front-Line Chemotherapy for Aggressive Non-Hodgkin's Lymphoma Using CAP-BOP With Doxorubicin (CB-A), Doxorubicin and Infusional Bleomycin/Vincristine (CB-AI), or Mitoxantrone (CB-M)

Julie M. Vose, MD*

Between September 1982 and January 1992, 389 patients with diffuse mixed-cell, diffuse large-cell, or immunoblastic non-Hodgkin's lymphoma (NHL) were treated with cyclophosphamide, procarbazine, and prednisone, with doxorubicin and bolus bleomycin and vincristine (CB-A), doxorubicin with infusional bleomycin and vincristine (CB-AI), or mitoxantrone with bolus bleomycin and vincristine (CB-M). The median age of all patients was 67 years (range, 15–92 years). Results at 2 years were as follows:

			Age ≤ 60 y		Age > 60 y	
Regimen	N	CR	OAS[1]	FFS**	OAS	FFS
CB-A	115	64%	70%	58%	42%	34%
CB-AI	138	66%	66%	54%	52%	39%
CB-M	136	65%	68%	62%	39%	30%

[1]OAS = overall survival; ** FFS = failure-free survival

Good-prognosis patients, who were aged ≤ 60 years, stage I or II, with a Karnofsky score ≥ 80, with a normal LDH, and with ≤ 1 extranodal site, had a 2-year survival of 100%, 82%, and 100% for CB-A, CB-AI, and CB-M, respectively. The incidences of pulmonary and cardiac toxicities were similar with each regimen, but the incidence of neurologic toxicity was higher with CB-AI than with the other two regimens (22% *vs* 10%; $P = 0.01$) and the incidence of alopecia was less with CB-M than with CB-A (38% *vs* 100%; $P < 0.01$). In older patients, a slight advantage in survival ($P = 0.08$), but not in disease-free survival, was observed in the CB-AI group compared with that in the CB-A group. Confirmation of any advantage of CB-AI will be necessary since its toxicity was higher. In younger patients, CB-M had a comparable treatment outcome to that with CB-A, but CB-M had less toxicity.

Full-Dose Chemotherapy in Elderly Patients With Intermediate/High-Grade Non-Hodgkin's Lymphoma: Interim Report of an Ongoing Study Comparing Doxorubicin and Mitoxantrone in a CHOP-Like Regimen

Pieter Sonneveld, MD, PhD*

An ongoing prospective study comparing four weekly schedules of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with CNOP (cyclophosphamide, mitoxantrone [10 mg/m²], vincristine, prednisone) in elderly patients (> 60 years) with intermediate/high-grade, stage II–IV, non-Hodgkin's lymphoma will be reported. A total of 151 patients (median age, 70.1 years) have been entered. An interim analysis of 110 evaluable patients, who have had a median follow-up of >12 months, indicates that high serum LDH levels, large tumor mass, extranodal disease, and stage IV disease are poor prognostic markers.

In the combined treatment groups, myelosuppression and cardiomyopathy were the prominent toxicities. A neutrophil count nadir of < 750 x 10^6/L was observed in 25% of the patients in course 1 and in 80% of the patients in course 6. A greater than 15% decrease in the left ventricular ejection fraction was observed in 47% of the patients, with evident clinical heart failure being present in 14% of the patients.

This study will provide further insight into the toxicity and efficacy of full-dose chemotherapy in elderly patients.

Mitoxantrone in Combination With Etoposide and Prednimustine (VMP) in Patients Older Than 70 Years With Unfavorable Non-Hodgkin's Lymphoma: A Prospective Study in 52 Patients

Umberto Tirelli, MD*

The optimal treatment of unfavorable non-Hodgkin's lymphoma (NHL) arising in the elderly population has not yet been codified, although it is clear that chemotherapy with a curative intent is indicated. Age is the most important adverse prognostic factor in NHL, based on several studies in patients usually aged less than 70 years; therefore, it is clear that NHL in patients aged 70 years and older is associated with a bad prognosis. Because of the criteria chosen to define a patient as elderly and the different inclusion criteria and treatments used in the studies of elderly patients reported in the literature, it is difficult to compare the results obtained by different groups.

Between January 1987 and April 1990, 52 consecutive unselected patients, aged older than 70 years (median age, 75.6 years) with stage I to IV, intermediate- and high-grade NHL or with stage III to IV, low-grade malignancy with symptomatic disease received etoposide and prednimustine, each at a dose of 80 mg/m² orally for 5 days, and mitoxantrone at a dose of 8 to 10 mg/m² intravenously on Day 1, which was repeated every 21 days. Fourteen of these patients had been treated previously. Among the 48 assessable patients, the objective response rate was 81%; 46% of the patients achieved a complete response (CR). The overall toxicity seemed to be acceptable, with 15 (7%) episodes of grade 4 leukopenia and 41 (18%) episodes of grade 3 leukopenia during a total of 226 administered cycles. The median duration of survival was 12 months. The patients who achieved a CR had a longer survival time than those who did not (34 *vs* 8 months; $P < 0.001$). Fifty-eight percent of patients who achieved a CR were free from relapse at 24 months, and 25% were free from relapse at 36 months after the start of therapy. In patients with diffuse histiocytic lymphoma, 66% of previously untreated patients obtained a CR, and 55% of these patients were still disease-free at 24 months after the start of therapy.

The VMP regimen was derived from two previous protocols of therapy for elderly patients with NHL (tenoposide alone and etoposide/prednimustine). The results of the present study demonstrate that VMP is an efficacious and well-tolerated regimen in a population of unselected elderly patients with unfavorable NHL. It must be stressed that no selection by age or performance status was made for patient entry into this study, as reflected by the median age of the patient population (75.6 years). The VMP regimen is feasible as an outpatient therapy in 95% of the cycles (only 10 cycles required hospitalization), a very important aspect to be considered in this elderly population. Extrahematologic toxicity was mild, and no cardiac toxicity was observed. Granulocyte colony-stimulating factor in combination with VMP is presently being studied to improve the bone marrow tolerance of the VMP regimen. Moreover, within the EORTC Lymphoma Group, a randomized trial comparing VMP versus CHOP in the elderly population with unfavorable NHL is ongoing.

PEN (Prednisone, Etoposide, and NOVANTRONE®) for Treatment of Non-Hodgkin's Lymphoma in Elderly Patients

Paul E. Goss, MB BCh, MRCP, FRCPC, PhD

Thirty-two patients (10 male, 22 female) aged 66–92 years (median age, 74 years) with non-Hodgkin's lymphoma (NHL) (Working Formulation C = 5, E = 1, F = 5, G = 16, H = 5) were treated every 28 days with PEN (prednisone 50 mg PO × 14 days, etoposide 50 mg PO × 14 days, and NOVANTRONE 8 mg/m² IV on Day 1). Twenty-one patients (66%) had previously untreated disease, and 11 (33%) had refractory NHL (7 nonresponders and 4 at relapse). Fourteen patients had stage IV, 14 had stage III, and 4 had stage II disease. Fifteen patients had B symptoms, 2 had extranodal disease, and 7 had bone marrow involvement. Patients with congestive heart failure, those receiving anti-failure medication or with a pretreatment Muga left ventricular ejection fraction of < 45% [median, 59% (n = 19)] were excluded from the study.

Of the 21 evaluable patients, 7 (33%) treatment-naive patients have achieved a complete response (4–68+ weeks), 4 (19%) have achieved a partial response (20–52+ weeks), and 3 are currently responding. One patient has not responded and 3 are not yet evaluable. The median survival time has not been reached, but 24 patients are alive 4–60+ weeks after the start of treatment.

During 135 courses of PEN, the median granulocyte count nadir was 0.66 × 10^9/L, occurring predominantly in the third (46%) and fourth (28%) weeks of the cycle. Seven patients had a granulocyte count nadir of < 0.5 × 10^9/L during at least one cycle, 4 of whom had bone marrow involvement. A platelet count nadir of < 100 × 10^9/L occurred in only two previously untreated and seven previously treated patients. Five episodes of febrile neutropenia requiring hospitalization occurred in four patients during the third and fourth weeks of either the first or second cycle. No treatment-related deaths occurred. Nonhematologic toxicity was minimal, with mild nausea, alopecia, and fatigue being the most common symptoms. In summary, PEN is an active, well-tolerated, ambulatory-care regimen for elderly patients with NHL. Enrollment in this trial is continuing.

MINE-ESHAP Salvage Therapy for Recurrent and Refractory Lymphomas

Fernando Cabanillas, MD*

Patients with recurrent or refractory lymphoma usually have a poor prognosis. Previous salvage regimens used at M.D. Anderson have been based either on ifosfamide/VP-16 or ara-C/platinum combinations. With these two regimens, complete response (CR) rates of approximately 20% were obtained, but less than 10% of all patients treated with these combinations were continuously disease-free for longer than 24 months. In 1988, a new strategy was developed that consisted of MINE (mesna, ifosfamide, NOVANTRONE, VP-16), which was given up to the maximum response and followed by consolidation with the non-cross-resistant ESHAP regimen (etoposide, Solu-Medrol, high-dose ara-C, platinum). Patients who attained a CR on MINE received six cycles and were consolidated with three cycles of ESHAP. Those who attained only a partial response (PR) on MINE were crossed over to ESHAP at the point of maximum response and received six courses of ESHAP. Response rates are summarized below:

	N	CR (%)	CR + PR (%)
All histologies	92	47	68
Intermediate/high-grade	42	43	60
Transformed	14	36	64
Low-grade	36	56	81

These CR rates are the highest that have been obtained with any salvage regimen at M.D. Anderson. The time-to-treatment failure also was significantly improved compared with that in previous studies; 18% of all patients with intermediate/high-grade disease are continously free of disease beyond 2 years compared with < 10% in previous studies. The survival was also superior. The results in the other cell types, including transformed lymphomas, also showed the same trends with respect to improved time-to-treatment failure and survival compared with previous regimens. MINE-ESHAP is effective in inducing remissions in most recurrent lymphomas. Although its curative potential is still not optimal, the remissions achieved are of a higher quality than those achieved with other salvage regimens.

Escalating Dose of Mitoxantrone With High-Dose Cyclophosphamide, Carmustine, and Etoposide (CBV) in Refractory Lymphoma Undergoing ABMT

Michel Attal, MD*

CBV (cyclophosphamide, carmustine, etoposide) is a standard regimen for patients with lymphoma who are undergoing autologous bone marrow transplantation (ABMT). However, almost all patients grafted in the refractory phase of the disease ultimately relapse. Mitoxantrone (MITO) is an active drug in lymphoma and has been demonstrated to be suitable for dose escalation when supported with ABMT. Thus, a dose-finding study of MITO was conducted in association with CBV and ABMT. The schedule was as follows: MITO, single infusion over 30 min on Day -8; cyclophosphamide, 1.5 g/m² on Days -7, -6, -5, -4; etoposide, 125 mg/m² every 12 hours for eight doses on Days -7, -6, -5, -4; carmustine, 300 mg/m² in a single bolus infusion on Day -4; and the unpurged bone marrow graft was infused on Day 0. Twenty patients (mean age, 38.5 years) with malignant lymphoma (Hodgkin's disease, n = 6; non-Hodgkin's lymphoma, n = 14), who were refractory to conventional therapy (primary refractory, n = 8; refractory relapse, n = 12), were treated at six dose levels of MITO (15, 30, 45, 60, 75, and 90 mg/m²).

Pharmacokinetic results demonstrated a linear relationship between the administered dose of MITO and 1) the plasma peak concentration, 2) the area under the curve, and 3) the Day 0 plasma concentration of MITO. No toxic deaths occurred. The maximum tolerated dose of MITO appeared to be 75 mg/m². Two of five patients treated with MITO 90 mg/m² developed a WHO grade toxicity ≥ 3 (1 hepatic, 1 cardiac) versus 0 of 15 patients treated with MITO doses ≤ 75 mg/m². Furthermore, the mean duration of neutropenia was 31.7 days for patients treated with MITO 90 mg/m² versus 22.6 days for MITO doses ≤ 75 mg/m² ($P < 0.05$). Hematologic toxicity appeared to be due to the long terminal plasma half-life of MITO, which resulted in the drug being detectable in plasma on the day of bone marrow infusion.

A high response rate was observed at each dose level of MITO, with 60% of patients achieving a complete response (CR). The 2-year, post-ABMT probability of survival was significantly higher for patients achieving CR after ABMT (71%; 95% CI = 30–99%) than for patients who did not achieve CR (0%) ($P < 0.001$). Finally, the high CR rate observed in this poor-risk population suggests that MITO plus CBV may represent an advance in the management of lymphoma.

New Aspects in the Treatment of Advanced Low-Grade Non-Hodgkin's Lymphomas: Prednimustine/Mitoxantrone (PmM) vs Cyclophosphamide/Vincristine/Prednisone (COP) Followed by Interferon Alfa vs Observation Only

Wolfgang Hiddemann, MD, PhD*

Following the promising report by Landys et al in 1988 on the high antilymphoma activity of PmM in high-risk, low-grade lymphoma, a Phase II study was initiated in patients with relapsed, low-grade, non-Hodgkin's lymphoma (NHL) using PmM for initial cytoreduction followed by interferon alfa-2b (IFN α-2b) maintenance therapy. Nineteen patients were treated according to this schedule and 13 (68%) responded, with four complete and nine partial remissions. All 13 responders subsequently received IFN α-2b maintenance treatment; a tendency toward a longer period of freedom from disease progression was observed when the duration of the second remission was compared with that of the preceding response.

Based on these data, a multicenter, randomized study was initiated comparing initial chemotherapy with PmM versus conventional COP in patients with untreated advanced centroblastic-centrocytic and centrocytic NHL. Patients who responded to 6–8 treatment cycles were randomized to IFN α-2b maintenance therapy versus observation only.

Presently, 226 patients have been entered and are eligible for response and toxicity analyses. The overall remission rate (CR + PR) was 83%. Myelotoxicity was the predominant side effect, occurring in 28% of the cycles with equal frequency after COP and PmM. PmM, however, caused significantly less peripheral neurotoxicity and alopecia than did COP. One hundred thirty-three patients have entered the second phase of therapy and have been randomized to IFN α-2b maintenance versus observation only. At the time of evaluation, no significant difference in the progression-free interval has been observed; the median duration of response has been 18 months.

These data indicate a high initial response rate to PmM and COP, although further follow-up is needed to assess the comparative efficacy of the two induction regimens. Additional patients and a longer follow-up are also needed to assess the final significance of IFN maintenance therapy.

Treatment of Hodgkin's Disease With the NOVP Regimen

Fredrick B. Hagemeister, MD

Treatment of clinically staged I–III Hodgkin's disease is in a state of evolution. For patients who have disease limited to the lymph nodes, a variety of different studies have demonstrated that survival appears to be very good regardless of the initial type of treatment administered, whether it be chemotherapy alone, radiation therapy alone, or combined-modality therapy. For this reason, the detection of patients who will have optimal results with initial therapy has become the main focus of modern treatment techniques. For a majority of patients, disease-free survival results appear to be better when chemotherapy is administered. However, chemotherapy has its drawbacks, including myelosuppression, sterility, and the risk of secondary malignancies.

In 1988, a study was begun in patients with stage I–III Hodgkin's disease, administering NOVP (NOVANTRONE 10 mg/m², Oncovin 1.4 mg/m², vinblastine 6 mg/m², prednisone 100 mg) followed by radiation therapy. To date, 106 patients have been accrued on this study. With a median follow-up of 20 months, the projected disease-free survival for patients with stages I and II disease at 3 years is 84%; for those with stage III disease, it is 76%. Overall survivals are 97% and 100%, respectively.

Tolerance to this new chemotherapy regimen has been excellent. Nausea/vomiting has occurred rarely, and was no more than grade 1 or 2. Significant alopecia has been rare. No male has become permanently sterile. Myelosuppression has been brief, with no observed thrombocytopenia and only one episode of hospitalization following the administration of chemotherapy. There has been no treatment-related mortality. One patient who developed melanoma 4 months after having completed radiation therapy has had it completely excised and is still free of disease.

Early results demonstrate that NOVP followed by radiation therapy is extremely well tolerated in patients with stage I–III Hodgkin's disease. These results also appear to be similar to those reported for patients receiving MOPP and radiotherapy, even for patients with large mediastinal adenopathy and other adverse features.

SATELLITE SYMPOSIUM

IL-3: EFFECTS ON THROMBOPOIESIS, MYELOPOIESIS AND BLOOD PROGENITOR CELL MOBILIZATION

Tuesday, June 8, 1993

Room B - 4:00-6:15 p.m.

IL-3 Effects on Thrombopoiesis, Myelopoiesis, and Mobilization of Peripheral Blood Progenitor Cells

Karen H. Antman, M.D., Dana-Farber Cancer Institute
Associate Professor of Medicine, Harvard Medical School

A number of hematopoietic growth factors have now been purified, cloned and produced in bacteria and yeast. G and GM-CSF enhance the recovery and function of circulating white cells after cytotoxic chemotherapy. However they do not significantly effect thrombocytopenia. IL-3, a second generation growth factor that acts on earlier hematopoietic progenitors, ameliorates both granulocytopenia and thrombocytopenia, alone or in combination with earlier (stem cell factor) or later acting (G or GM-CSF) hematopoietins in the laboratory. Early clinical trials are encouraging with enhancement of myelopoiesis and thrombopoiesis and mobilization of peripheral blood progenitor cells for hematopoietic support after dose intensive therapy. The IL-3 gene is found on chromosome 5q, the location of a cluster of genes involved in hematopoietic regulation (GM-CSF, IL-3, M-CSF and M-CSF receptor, IL-4, IL-5, and the receptor for PDGF) Deletion of this region, (5q-) is associated with various hematopoietic disease states. The optimal combination and sequence of cytokines for both myeloid and megakaryocytic recovery after conventional or high dose therapy or for mobilizing circulating hematopoietic stem cells is not yet established. Almost certainly a combination will prove most efficient. The ability to culture human hematopoietic stem cells ex vivo and to use these cultured cells for support after conventional dose or high dose therapy or even gene therapy will be a reality within a decade. Thus, growth factors are proving to be a significant addition to the clinicians' armamentarium. In addition they provide laboratory researchers with new tools for examining the process of hematopoiesis, clinically and at the molecular level.

INTERLEUKIN-3 (IL-3) IN VIVO: KINETIC OF RESPONSE OF TARGET CELLS.

Aglietta M. Clinica Medica Generale, Ospedale Maggiore, 28100 Novara, ITALY.

IL-3, human (Sandoz AG, Basel) was administered for 7 days to neoplastic patients with normal hemopoiesis. Study purpose was to assess IL-3 toxicity, to identify target cells and to define their kinetics of response at different dose levels, and finally to determine if IL-3 in vivo increased the sensitivity of bone marrow (BM) progenitors to the action of other hemopoietic growth factors. Twenty one patients entered the study; the dosage ranged from 0.25 to 10 μg/Kg/day.

Effect on peripheral blood cells: During treatment no changes in the number of platelets, erythrocytes, neutrophils, lymphocytes were observed. A mild monocytosis and basophilia occurred. Eosinopenia, present in the first hours of treatment, was followed by a dose and time dependent eosinophilia.

Effect on BM cell proliferation: IL-3 treatment increased the percentage of BM progenitors engaged in the S-phase of the cell cycle. The effect was dose dependent with the various progenitors showing different degrees of sensitivity: the most sensitive were the megakaryocyte progenitors (CFU-MK), followed by the erythroid (BFU-E) and finally by the granulo-monocyte (CFU-GM) progenitors. Only a slight increase in the proliferative activity of myeloblasts, promyelocytes and myelocytes was observed, whilst that of erythroblasts was unchanged.

Priming effect: BM progenitors, purified from patients treated with IL-3, produce more colonies, in vitro, in the presence of G-CSF (granulocyte colonies), IL-5 (eosinophil colonies), GM-CSF (predominantly eosinophil colonies). These data indicate that even in vivo, IL-3 acts essentially as a primer for the action of other cytokines. Therefore, optimum stimulus of myelopoiesis will require either endogenous or exogenous late acting cytokines such as G-CSF, Erythropoietin, GM-CSF, IL-6 for achieving fully mature cells in peripheral blood. If exogenous cytokines are used with IL-3, it is likely that G-CSF will yield more neutrophils, whereas GM-CSF may enhance eosinophils, monocytes and neutrophils.

PHASE I/II DOSE-FINDING STUDY OF INTERLEUKIN-3 IN RELAPSED LYMPHOMAS TREATED WITH IEV CHEMOTHERAPY.

H.H. Gerhartz, J. Walther, P. Klener, C. Peschl, C. Huber, G. Visani, W. Wilmanns, R. Mull, I. Sklenar. Med. Dept. III, Klinikum Großhadern, Munich Univ., D 8000 Munich 70; Charles Univ. Prague; III Med. Dept., Mainz Univ.; Dept. Hematol., Bologna Univ.; and Sandoz Ltd., CH 4002 Basle.

Patients with aggressive lymphomas (17 Non Hodgkin lymphomas - NHL, 11 Hodgkin's disease - HD) resistant to previous rescue chemotherapy (ctx, n=23) or in first relapse (n=5) were treated with the IEV regimen (ifosfamide 2.5 g/m^2 q 3 days, epirubicine 50 mg/m^2 q 1 day, etoposide 100 mg/m^2 q 3 days) followed by IL-3 s.c. at various doses (2.5, 5.0, 10.0 and 15.0 μg/kg) and schedules (5 or 10 days). All pts were pretreated (2-3 different regimens, 16 with additional radiotherapy) and in advanced stage. A total number of 69 courses (2-3 per patients) was given. Neutrophil- and platelet recovery was faster in pts recieving 10-15μg/kg IL-3 as compared to lower doses. The median duration of neutropenia (ANC < 1.0 x 10^9/l) was 6 ±4 days with absence of neutropenia in patients receiving the highest IL-3 dose (15 μg/kg b.w.). The median number of thrombopenia (platelets <50 x 10^9/l) was 3.5 ± 7 days with absence of thrombopenia in patients receiving 10-15 μg/kg IL-3 (29 of 69 courses). Platelet transfusions were necessary in 14/69 courses. The rate of infections was low (10 WHO grade 1-2, 1 WHO grade 4), hemorrhage occured only once (WHO grade 1). Adverse events associated with IL-3 were fever (n=18), dyspnoea (n=3), chills (n=5), local cutaneous reactions (n=4), transient pericardial effusion (n=2), headache (n=4) and transient tachycardia (n=2). Response was evaluable in 25 pts (NHL: 3 CR, 6 PR, 6 NC; HD: 5 CR, 5 PR) with durations up to 2 years so far. Circulating progenitor cells were transiently elevated up to 1000 fold. Cytokine levels were measused in sera of the patients (GM-CSF, IL-6 and TNFα): 3 cases showed transient increases of IL-6 associated with IL-3 administration. Statistically, elevated levels of GM-CSF were associated with a shorter duration of neutropenia, higher temperatures and occurence of adverse events. IL-6 levels were correlated to the occurence of infections whereas high TNFα levels during the last course indicated a poor response. These data show that a dose-dependent effect of IL-3 on plateled and neutrophil recovery. IEV ctx plus IL-3 is well tolerated and effective in patients with resistant aggressive lymphomas.

HUMAN RECOMBINANT INTERLEUKIN-3 (IL-3) AFTER AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) FOR MALIGNANT LYMPHOMA.

W.E. Fibbe, J.Raemaekers, L.F. Verdonck, H.C. Schouten, G. van Imhof, B. Tromp, R. Willemze, J. van Bree, J.A. Hessels, and E. Vellenga. Department of Hematology, University Medical Center Leiden, the Netherlands and Sandoz Pharma, Basle, Switzerland.

We evaluated the efficacy and toxicity of human recombinant IL-3 (Sandoz Pharma) administered after ABMT for malignant lymphoma. Twenty-four patients with non-Hodgkins lymphoma (NHL) or Hodgkin's disease (HD) in second or subsequent remission received ABMT after conditioning with BCNU, Etoposide, Ara-C, Cyclophosphamide (NHL) or Cyclophosphamide, BCNU, Etoposide (HD). From day one after marrow infusion, patients were treated with IL-3 by continuous infusion for 14 days at doses ranging from 0.25 (n=6), 5 (n=4), 10 (n=10) and 15 μg/kg body weight/day (n=4). Five patients, eligible for the study but not treated with IL-3, served as controls. As of the day of writing the data from 16 patients who completed IL-3 treatment (8 males, 6 females, NHL n=5, HD n=9, median age 32 years, range 18-58), were evaluated. All patients engrafted. The median time to reach a neutrophil count of 0.5 x 10^9/l or a platelet count >50 x 10^9/l was 22 days (range 11-28) and 23 days (range 15-35) respectively for 6 patients treated with 10 μg/kg IL-3 versus 27 days (range 13- >40) and 30 days (range 11- >40) for 5 patients receiving no or 0.25 μg/kg IL-3. For the IL-3 (10 μg/kg) treated patients the median time to reach 1% reticulocytes was 22 days (range 14-40) versus 40 days (range 21-40) for those receiving no or 0.25 μg/kg IL-3. Side effects of IL-3 (>= 5 μg/kg) included facial flushing (3/16), headache (8/16) and fever (WHO grade 2 and 3) that required discontinuation in 1/6 and 3/4 patients treated with a dose of 10 μg/kg and 15 μg/kg respectively. In patients with grade 3 fever circulating IL-6 levels were significantly higher (> 1000 U/ml) then in patients without fever (< 20 U/ml) or with grade 1/2 fever (40 U/ml). These preliminary data indicate that 1) IL-3 treatment at a dose of 10 μg/kg daily may accelerate the reconstitution of neutrophils and platelets after ABMT for malignant lymphoma 2) Dose-limiting side effects occur at a dose of 15 μg/kg/day 3) Fever induced during IL-3 treatment may be mediated by Interleukin-6. During the meeting the results of 38 patients will be presented. A phase III study is ongoing to further evaluate the efficacy of IL-3 in the setting of ABMT.

MOBILISATION OF PERIPHERAL BLOOD AND EX VIVO EXPANSION OF HAEMOPOIETIC CELLS WITH CYTOKINES. C.A. Juttner, L.B. To, D.N. Haylock, P.G. Dyson, J. Bayly, C. Rawling, P.J. Simmons. Hanson Centre for Cancer Research and Royal Adelaide Hospital, Adelaide, South Australia.

PBSC Mobilisation

Mobilised or perturbed peripheral blood stem cells (PBSC) and progenitor cells produce haemopoietic reconstitution after high dose therapy and autologous rescue which is between 7 and 10 days faster than autologous or allogeneic bone marrow, with consequent reductions in periods of hospitalisation, infection, intensity of support and most importantly, costs.

Initial mobilisation techniques used the recovery period from myelosuppressive chemotherapy. This demonstrated efficacy but was associated with heterogeneity of response and some morbidity and even mortality. Later mobilisation techniques used cytokines, particularly granulocyte-macrophage colony stimulating factor (GM-CSF) in association with chemotherapy. This produced higher yields of PBSC and a less heterogeneous response. Subsequent studies using granulocyte colony stimulating factor (G-CSF) alone also demonstrate efficacy and may allow possible application of PBSC rescue techniques to allogeneic recipients whose normal donors clearly should not receive myelosuppressive chemotherapy.

Current directions of research in PBSC mobilisation and transplantation include optimisation of combinations of chemotherapy with cytokines, optimisation of cytokine schedules when cytokines are used alone without chemotherapy, and optimisation of combinations of cytokines used together, both dose and schedule.

Ex-Vivo Expansion

The current best haemopoietic reconstitution after high dose therapy and transplantation appears to result from the use of optimally mobilised peripheral blood stem cells with or without bone marrow, with or without post graft colony stimulating factor. This does not permit total abrogation of neutropenia and thrombocytopenia and there is currently a mandatory period of significant risk-associated cytopenia of approximately 3-9 days. Newer approaches currently under study examine the potential for total abrogation of this dangerous period of cytopenia using cells expanded outside the body with combinations of cytokines. The approach appears feasible and there is some animal data to suggest efficacy. Clinical studies should commence in the latter part of 1993.

CLINICAL EFFECT OF INTERLEUKIN-3 (IL-3) ALONE AND COMBINATIONS OF IL-3/GM-CSF AND IL-3/G-CSF IN NON-HODGKIN LYMPHOMA.
D. Hovgaard, N.I. Nissen, Dept. of Hematology, Rigshospitalet, Copenhagen Denmark.

42 previously untreated patients with newly diagnosed non-Hodgkin lymphoma were treated with standard CHOP chemotherapy in combination with cytokines. In 24 patients IL-3 was given s.c. as monotherapy for 14 days following CHOP cycle 2 and 4 and after cycle 6 in combination with GM-CSF (3 μg/kg). Four dose levels of IL-3 were examined, 0.5, 1.0, 5.0 and 10 μg/kg. In groups of 6 patients, combinations of IL-3 (7.5 μg /kg) and GM-CSF (3 μg/kg) and IL-3 (7.5 μg/kg) and G-CSF (3 μg/kg) either as sequential or simultaneous administration were examined.
Monotherapy with IL-3 was well tolerated with minor to moderate side effects, fever, chills, cutaneous reactions and flu-like symptoms. These were more pronounced following combination therapy. Preliminary results showed an increase on day 5 (mean) of WBC, espec. neutrophils, following monotherapy of IL-3 and all the different combinations. The counts at the nadir, day 9 (mean) were higher, in particular following IL-3 and G-CSF. Day of nadir was earlier during cytokine therapy compared to control cycles and the neutropenic period was reduced in cycles with cytokines. An increase on day 15 of WBC and neutrophils compared to control cycles was noted during cytokine therapy, espec. for combinations including G-CSF. Recovery from day 15-22 of WBC and neutrophils was also increased, espec. after IL-3 monotherapy or combinations of IL-3 and GM-CSF. Platelet counts were increased in the recovery period day 15-22, when IL-3 was administered alone or combinations of IL-3 and GM-CSF.

SATELLITE SYMPOSIUM

INTERFERON - ALFA UND
G - CSF IN DER HÄMATOLOGIE

(language: German)

Thursday, June 10, 1993

Room B - 6:30-8:15 p.m.

α-INTERFERON IN THE TREATMENT OF FOLLICULAR LYMPHOMA. F. Cavalli, Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland

Follicular lymphomas are considered an incurable disease, even if long-term results with newer approaches (e.g. ABMT) have still to be awaited. There is no international agreement on the exact role of prognostic factors, but several studies have shown that adverse prognostic factors for large-cell lymphomas are also associated with a poor prognosis in follicular lymphoma patients.
In this set, Interferon has shown in phase II trials a response of 30-50 %, both in previously treated and untreated patients, whatever the Interferon subtype was used.
The real question today is what Interferon can do in the maintenance phase of the treatment. Today, 5 prospective studies have sufficiently matured to be discussed.
Two American studies were recently published (Ann Oncol 4: 205, 1993 and NEJM 327: 1335, 1992). Both studies have some methodological drawbacks, mainly that all low-grade lymphomas were entered and not only patients with follicular lymphomas. Probably more interesting are 3 European studies with the EORTC trial and the French study of the GELA group will be presented in a new analysis at this conference. Basically they support the conclusion of the third European study (the well known Bartholomew's study, presented in great details at the last Lugano Conference): α-Interferon prolongs disease-free survival, whereas it remains to be seen whether overall survival will also be prolonged. Only the GELA study shows for the time being a clearcut benefit in terms of overall survival.

ALPHA-INTERFERON FOR THE TREATMENT OF MULTIPLE MYELOMA. R. Herrmann. Division of Oncology, Departement of Medicine, Kantonsspital (University hospitals), CH-4031 Basel.

Recombinant α-Interferon has shown antiproliferative activity against myeloma cells in vitro. In clinical studies α-Interferon has been evaluated for various stages and situations. As single agent it has been used for stage I disease with equivocal results on the production of paraproteins. In stage II/III disease α-Interferon as single agent can produce remissions in about 25% of previously untreated patients which, however, is inferior to the results achieved with chemotherapy. In previously treated myeloma, single agent α-Interferon may achieve a remission in 10 - 15% of patients. In combination with Melphalan/Prednisone α-Interferon has been found to be superior to chemotherapy alone in one study and equally effective in another study for previously untreated patients. In a third study the alternating application of chemotherapy and α-Interferon has proven to be significantly better than chemotherapy alone indicating that scheduling may be important.About 1/3 of previously treated patients will benefit from α-Interferon in combination with chemotherapy or glucocorticoids. Following successful induction chemotherapy, treatment with α-Interferon has been able to significantly prolong progression free survival compared to no maintenance treatment. In conclusion, α-Interferon seems to be effective in prolonging duration of remission. Results on the use of α-Interferon in combination with chemotherapy for remission induction are conflicting and may require exploration of other schedules.

INTERFERON IN THE TREATMENT OF CML: UPDATE OF THE ITALIAN RANDOMIZED STUDY. S. Tura on behalf of ICSG-CML. Institute of Hematology, University of Bologna, Via Massarenti 9, 40128 Bologna, Italy.

On the basis of preliminary results obtained at the MD Anderson Cancer Centre in Houston in early '80 (1), the Italian Cooperative Study Group on CML proposed a long-term prospective comparative study of interferon-alpha-2a (IFN-α2a) versus chemotherapy in chronic phase CML which started in June 1986.
A total of 322 Philadelphia-chromosome positive (Ph^+) patients collected by 46 centres across Italy, who had received no treatment or minimal treatment prior to trial entry, were included in the trial. Of these patients, 218 received IFN-α, while 104 were treated with hydroxyurea. Patients were randomized to each group prior to treatment, in a ratio of 2:1. Hematologic response was similar in the 2 groups (over 80%) but complete hematologic response was higher in the IFN-α than in chemotherapy group (34-38% vs. 4-20%). More interestingly, the karyotypic response was quite different in the 2 groups. An overall response rate of more than 60% was observed in the IFN-α group, versus less than 50% in the chemotherapy group. Moreover, the quality of the karyotypic conversion was different: a karyotypic conversion >33% (that is more than 33% of Ph^1-negative metaphases) was observed in 16% of IFN-treated patients vs 1% of chemotherapy treated ones after 8 months, in 24% vs 4% after 24 months and in 37% vs 4% after 48 months, respectively. Survival of IFN-treated patients was significantly longer than that of CHT treated ones. Median survival was not yet reached by the former group after 60 months of treatment, while it was of 49 months in the latter. The difference in survival was significant particularly in higher risk patients (58 vs 38 months, respectively, p=0.0002) (2). The best prognostic indicator for karyotypic response was the degree of karyotypic conversion. Among the 34 patients who acheived a major+complete karyotypic conversion, only 1 developed blastic transformation.
Survival rate according to karyotypic conversion at 60 months was 96% for major+complete responses, 70% for minor responses and 38% for minimal or no conversion (3).
IFN-α therapy was discontinued in 21% of the patients, either for side effects (14%) or refusal (7%). With regards to side-effects most patients experienced a flu-like syndrome in the first 3 months of treatment. Definitive discontinuation was predominantly due to gastrointestinal, neurologic or hematologic toxicity.
Sixty blastic metamorphoses, occurred out of the 218 patients of the IFN-α arm, vs 39 out of 104 of the CHT arm (p=0.08). In this series, the prevalence of lymphoid blastic crises observed among the IFN treated patients, reported by other groups, was not observed. The survival advantage occurred in a fully randomized group of patients who had not been selected as being most likely to respond well to treatment prior to starting IFN-α therapy. These results should thus closely match the response in a non-trial setting.

References

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Application of hematopoietic growth factors in hemato-oncology. A. Tobler. Central Hematology Laboratory University of Berne, Inselspital, CH-3010 Berne, Switzerland.

Numerous hematopoietic growth factors, also known as hematopoietic cytokines, have been molecularly cloned and purified to homogeneity. We have learned from *in vitro* studies that 1) hematopoietic growth factors are important for proliferation and development of stem cells, as well as for function and by preventing apoptosis for survival of more mature cell populations; 2) hematopoietic growth factors share common target cells; 3) they synergize with each other; 4) in addition to growth stimulatory factors cytokines have been identified which inhibit hematopoietic stem and progenitor cells (e.g. TGFβ, MIP-1α/SCI); 5) both growth stimulatory and inhibitory cytokines are produced by normal hematopoietic cells upon stimulation and constitutively by leukemic cells, as well as by accessory bone marrow cells which constitute the hematopoietic microenvironment. Thus, hematopoietic cytokines comprise a complex interacting network. Two hematopoietic growth factors, G-CSF and GM-CSF, have been extensively studied in clinical phase I-III trials. Both agents are effective in increasing neutrophils counts and are relatively well tolerated when given by continuous i/v or bolus s/c infusions at doses of 3-10 µg/kg/d. Most trials, either in the setting of intensive chemotherapy of solid tumors, or in that of autologous or allogeneic bone marrow transplantation have shown that G-CSF or GM-CSF decrease the days of neutropenia, of antibiotics and of hospital stay. However, with the current schedules applied the neutropenic phase could not be abrogated, and also thrombocytopenia remains a problem. In addition, no survival improvement was noted. IL-3, which exhibits multilineage actions, has increased in some patients, but not consistently, thrombocyte counts. The combinations of IL-3 with thrombopoietic factors such as IL-6 or IL-11 may help to substantially improve thrombocyte recovery. Another rapidly expanding field of hematopoietic growth factor application is their use in peripheral blood stem cell mobilization. Myelosuppressive chemotherapy and/or CSF such as G-CSF or GM-CSF transiently increase the number of circulating stem and progenitor cells. As compared with autologous marrow transplantation accelerated marrow reconstitution has been observed when G-CSF or GM-CSF mobilized peripheral blood stem cells were reinfused after myeloablative treatment. (The presentation will be in German)

CONTROLLED STUDY OF FILGRASTIM AFTER HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR HIGH RISK LYMPHOMA.

R.A. Stahel, L.M. Jost, G. Pichert, T. Cerny, H.P. Honegger, E. Jacky, M. Fey, and E. Platzer. Division of Oncology, Department of Medicine, University Hospital, Zürich, Institute of Oncology, Inselspital Bern and Amgen-Roche, Basel, Switzerland.

We report on a randomized controlled study on the tolerance and efficacy of filgrastim in patients with high risk lymphomas treated with high dose cyclophosphamide, BCNU and etoposide and autologous bone marrow transplantation (ABMT). Patients were randomized to receive filgrastim by continuous subcutaneous infusion at doses of 10 or 20 µg/kg/day starting on day 1 after ABMT or to control receiving no filgrastim. Of 44 patients entering the study, 43 were evaluable. Twenty-nine received filgrastim (10 at 20 and 19 at 10 µg/kg/day) and 14 were in the control group. Thirty-one patients had non-Hodgkin's and 12 Hodgkin's lymphoma. The median time to neutrophil recovery of $\geq 0.5 \times 10^9$/l was 10.0 days for all patients receiving filgrastim taken together and 18.0 days for the control patients (p=0.0001). Neutrophil recovery was very similar between patients treated with 20 µg/kg/day and 10 µg/kg/day. The median number of days with fever >38.2° was 1.0 (range 0-9) in the filgrastim group and 4.0 (range 0-8) in the control group (p=0.0418). Filgrastim treatment resulted in a significant reduction of days with febrile neutropenia with 5.0 (range 0-14) in the filgrastim group and 13.5 (range 0-32) in the control group (p=0.001). This difference was maintained, when patients treated at 10 µg/kg/day were compared to control patients (0.0001). Patients treated with filgrastim had less days on intravenous antibiotics than control patients (8.0 vs 12.5 days), this difference did not reach statistical significance (p=0.0528). The rate of documented infections was 86% in the filgrastim and 100% in the control group. By day 15 after ABMT 37% of the filgrastim treated patients, but none of the control patients, were discharged from the hospital. The median time of hospitalization after ABMT was 18.0 days in the filgrastim group and 21.0 days in the control group (p=0.214). Severe bone pain in one patient and a moderate local skin reaction in another patient were the only events considered to be definitively related to filgrastim. The former disappeared after dose reduction and the skin reaction did not preclude continuation of filgrastim therapy. No patient died during high dose chemotherapy and ABMT. Analysis of survival after discharge gave no evidence for a detrimental effect of filgrastim. Based on our results we conclude that filgrastim at a dose of 10 µg/kg is safe and effective in accelerating hematopoietic recovery after high dose chemotherapy and ABMT and significantly reduces morbidity as measured by the number of days with febrile neutropenia and fever.

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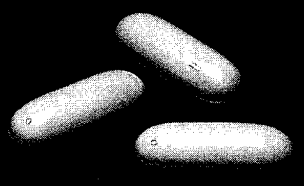

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