SATELLITE SYMPOSIA
SATELLITE SYMPOSIUM

LONG-TERM RESULTS & CLINICAL PROGRESS IN LYMPHOMA THERAPY

Tuesday, June 8, 1993
Room A - 1:30-5:30 p.m.
ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano

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

Werner K. Beuscha, M.D., M.O., P.P.S.A., F.L.B.C.

A randomized, multicenter, phase III trial was conducted to compare the efficacy and safety of the CHOP and CNOX 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 days 1 to 5. The CNOX regimen was identical to CHOP, except that vincristine 10 mg/m² was substituted for doxorubicin. A total of 399 patients were accrued; 595 were appropriately randomized and were included in the efficacy and survival analysis. 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 CHOP group than in the CNOX group, and there were more patients with stage III disease in the CNOX group than in the CHOP group. Furthermore, the stage IV patients were slightly more in the intermediate-grade class in the CHOP group than in the CNOX group and slightly more patients with high-grade NHL in the CHOP group than in the CNOX group.

Eighty-nine of the 164 patients (54%) randomized to the CHOP regimen achieved complete remissions (CR) compared with 64 of 164 patients (41%) randomized to receive CNOX (P = 0.049). An additional 23 patients in the CHOP group and 25 patients in the CNOX group achieved partial remissions, resulting in overall response rates of 69% and 60%, respectively (P = 0.22). The median duration of CR was 667 days in patients receiving the CHOP regimen compared with 1335 days in those receiving the CNOX regimen. The median survival was 952 days (range, 0–2490 days) for CHOP and 1611 days (range, 0–2379 days) for CNOX-treated patients (P = 0.68, hazard ratio, 0.93). The median duration of follow-up was 490 days (range, 0–2583 days) for patients in the CHOP group and 493 days (range, 0–2813 days) for patients in the CNOX group. At the end of 5 years, 50% of patients in the CHOP and 40% of patients in the CNOX group were still alive. The more common cause of death was disease progression.

The number of patients experiencing at least one severe adverse event, regardless of severity, was similar in the two treatment groups. However, a significantly higher number of patients receiving CHOP (9% vs 4%) experienced severe nausea and vomiting, alopecia, and mucositis compared with those receiving CNOX. Severe neutropenia occurred in 40% of the CHOP courses compared with 30% of the CNOX courses. However, the differences in incidence of neutropenia did not appear to have any clinical impact since the incidence and severity of infection were similar in the two treatment groups. It was concluded that both the CHOP and CNOX regimens are effective and less severe adverse events are associated with the CHOP regimen.

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, M.D., Ph.D.

An ongoing prospective study comparing four weekly schedules of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with CNOX (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 191 patients (mean age, 76.5 years) have been entered. An interim analysis of 118 evaluable patients who have had a median follow-up of 11.3 months, showed 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 cardiotoxicity were the prominent toxicities. A mean 3rd count nadir of ≤ 750 × 10⁹/μl was observed in 29% of the patients in course 1 and in 38% of the patients in course 6. A greater than 10% decrease in the platelet count nadir 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.

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

Julie M. Vose, M.D.

Between September 1982 and January 1992, 398 patients with diffuse mixed-cell, diffuse large-cell, or immunoblastic non-Hodgkin’s lymphoma (NHL) were treated with cyclophosphamide, doxorubicin, and prednisone, with doxorubicin and bleomycin vincristine (CB-A), doxorubicin and bleomycin vincristine (CB-AB), or mitoxantrone with bleomycin vincristine (CB-M). The median age at all patients was 61 years (range, 15-92 years). Results at 2 years were as follows:

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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 Tiribilli, M.D.

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 cisplatin-based regimen is indicated. Age is the most important adverse prognostic factor in NHL, based on several studies in patients 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 an 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 1999, 52 consecutive untreated 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 symmetric disease restricted extralymphatic and extramedullary, such as a dose of 80 mg/m² for 5 days, and mitoxantrone as a dose of 8 to 10 mg/m² intravenously on Day 1, which was repeated every 21 days. Fourteen of these patients had been previoudly treated. Among the 46 assessable patients, the objective response rate was 81%, 60% of the patients achieved a complete response (CR). The overall toxicity seemed to be acceptable, with 15 (36%) episodes of grade 4 thrombocytopenia and 41 (90%) episodes of grade 3 thrombocytopenia during a total of 236 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 CR at 8 months (P = 0.003). 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, 60% of previously untreated patients achieved a CR, and 55% of those 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 (comers of doxorubicin and prednimustine). The results of the present study demonstrate that VMP is an effective and well-tolerated regimen in a population of untreated elderly patients with unfavorable NHL. It must be pointed out that no current or at-risk performance status was made for patient entry into this study, as indicated by the median age of the patient population (75.6 years). The VMP regimen is feasible as an effective and well-tolerated regimen in elderly patients with unfavorable NHL, and it is currently being studied in the elderly population with unfavorable NHL and NHL.
ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano

PEN (Prednisone, Etoposide, and NOVANTRONE*) for Treatment of Non-Hodgkin’s Lymphoma in Elderly Patients
Paul E. Goss, MB BCh, MRCp, FRCP, PhD

Thirty-two patients (19 male, 23 female) aged 65–92 years (median age, 75 years) with non-Hodgkin’s lymphoma (NHL) (Working Formulation: C = 3, E = 1, F = 3, G = 16, H = 6, S = 1) were treated every 28 days with PEN (prednisone 50 mg PO X 14 days, etoposide 50 mg PO X 14 days, and NOVANTRONE 8 mg/m² IV on Day 1). Twenty-one patients (66%) had previously untreated disease, and 11 (34%) had relapsed NHL. All patients had stage IV, 14 had stage III, and 4 had stage II disease. Fifteen patients had 3 lymphomas, 3 had extranodal disease, and 7 had bone marrow involvement. Patients with congestive heart failure, those receiving anti-arrhythmic medication or with a pretreatment left ventricular ejection fraction of < 40% (mean, 59% ± 10%) were excluded from the study.

Of the 21 evaluable patients, 7 (33%) were evaluable. All 7 patients have achieved a complex response (4+ week), 4 (19%) have achieved a partial response (5+2 week), 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 4 patients are alive 4+ weeks after the start of PEN. During 150 cycles of PEN, the median granulocyte count nadir was 0.66 x 10⁹/L, occurring predomi-
nantly in the third (24%) and fourth (48%) weeks of the cycle. Seven patients had a granulocyte count nadir of ≤ 0.5 x 10⁹/L within 30 days of the start of PEN. Four patients had a granulocyte count nadir of ≤ 0.3 x 10⁹/L within 30 days of the start of PEN. Four patients had a granulocyte count nadir of ≤ 0.1 x 10⁹/L within 30 days of the start of PEN. Four patients had a granulocyte count nadir of ≤ 0.01 x 10⁹/L within 30 days of the start of PEN.

In summary, PEN is active, well-tolerated, and benefit-risk ratio is reasonable for elderly patients with NHL. Enrollment in this trial is continuing.

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 standard regimen for patients with lymphoma who are undergoing intensive bone marrow transplantation (ABMT). However, almost all patients gradiated in the hematologic and neurologic phase of the disease ultimately relapse. Mitoxantrone (MTO) is an active drug in lymphoma and refractory phase of the disease. A study was conducted in association with ABMT. Thus, a dose-escalation study of MTO was conducted in association with CBV and ABMT. The schedule was as follows: ABMT; 125 mg/m² every 12 hours for eight doses on Day 1, 15 mg/m² every 12 hours for eight doses on Day 2, 15 mg/m² every 12 hours for eight doses on Day 3, 15 mg/m² every 12 hours for eight doses on Day 4, and the unprocessed bone marrow graft was infused on Day 6. Twenty patients (mean age, 38.5 years) with malignant lymphomas (MTO, n = 6; non-Hodgkin’s lymphoma, n = 14), who were refractory to conventional therapy (primary refractoriness, n = 1; relapse refractoriness, n = 12), were treated at six dose levels of MTO (10, 15, 20, 40, 75, and 90 mg/m²).

Pharmacokinetic and clinical results demonstrated a linear relationship between the administered dose of MTO and the plasma peak concentration. The area under the curve, and the peak plasma concentration of MTO were the main factors. The maximum tolerated dose of MTO increased to 90 mg/m² in the dose group. Two of five patients treated with MTO 90 mg/m² developed a WHO grade toxicity: 3 (lethargy, 1 cardiac). Four of 15 patients treated with MTO 75 mg/m² had low-grade toxicity. The major dose-limiting toxicity was grade 3/4 neutropenia for 5–17 days for patients treated with MTO 90 mg/m² versus 9–24 days for MTO doses ≤ 75 mg/m² (P = 0.05). Hematologic toxicity appeared to be due to the long-term exposure to MTO, 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 MTO, 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 (10%, 59%, CI = 0–99%) than for patients who did not achieve CR (9%) (P = 0.03). Finally, the high CR rate observed in the prospective population suggests that MTO plus CBV may represent an advance in the management of lymphoma.

MINE-ESHAP Salvage Therapy for Recurrent and Refractory Lymphomas
Fernando Cabanillas, MD

Patients with relapsed or refractory lymphoma usually have a poor prognosis. Previous salvage regimens used at M.D. Anderson have been based either on fludarabine-VP-16 or cyclophosphamide combinations. With these two regimens, complete response (CR) rates of approximately 20% were obtained, but less than 10% of all patients relapsed with these combinations. The current study was designed to evaluate the efficacy of a new combination therapy, MINE-ESHAP (mitoxantrone, ifosfamide, vincristine, epirubicin, cyclophosphamide, and prednisone). In the past, the MINE-ESHAP regimen has been associated with a high incidence of chemotherapy-related toxicities. We evaluated the efficacy and toxicity of our regimen in 56 consecutive patients with relapsed or refractory lymphoma.

The CR and partial response (PR) rates were 62% and 19%, respectively. The median response duration was 43 weeks. The overall CR rate was 80%, and the median progression-free survival was 6 months. The study demonstrates that MINE-ESHAP is an effective salvage therapy for patients with relapsed or refractory lymphoma.

New Aspects in the Treatment of Advanced Low-Grade Non-Hodgkin’s Lymphoma: Prednimustine/Mitoxantrone (PmM) vs Cyclophosphamide/Vincristine/Prednisone (COP) Followed by Interferon Alfa vs Observation Only
Wolfgang Hiddemann, MD, PhD

Following the preceding report by Facon et al. in 1988 on the high melphalan activity of PMH in high-grade, low-grade lymphoma, a Phase II study was initiated in patients with relapsed, low-grade, non-Hodgkin’s lymphoma (NHL) using PMH as initial reinduction followed by interferon alfa-2b (IFN-2b) as maintenance therapy. Seventeen patients were treated according to the schedule and 13 (88%) responded, with four complete and nine partial remissions. All 13 responders subsequently received 93% of IFN-2b maintenance courses, a registry 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 PMH versus conventional COP in patients with uncontrolled advanced histiocytic and non-Histiocytic NHL. Patients who responded to 6-8 treatment courses were randomized to IFN-2b maintenance therapy versus observation only.

Previously, 262 patients have been entered and are eligible for response and toxicity analyses. The overall remission rate (CR + PR) was 45%. Morbidity was the predominant side effect, occurring in 28% of the cycles with equal frequency after COP and PMH. However, the initial study was performed with highly active COP, which was associated with a high incidence of side effects. In the second phase of therapy and have been randomized to IFN-2b maintenance versus observation only. At the time of evaluation, no significant difference in the progression-free survival has been observed; the median duration of response has been 28 months.

These data indicate a high initial response rate to PMH 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 needed to assess the final significance of IFN-2b maintenance therapy.
Treatment of Hodgkin's Disease With the NOVP Regimen

Frederick R. Hagemetser, MD

Treatment of clinically staged I-IIIA 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-IIIA Hodgkin's disease, administering NOVP (nitrogen mustard 10 mg/m², vincristine 1.4 mg/m², procarbazine 100 mg/m²) followed by radiation therapy. To date, 106 patients have been accrued on this study. With a median follow-up of 30 months, the projected disease-free survival for patients with stages I and II disease at 5 years is 84%; for those with stage III disease, it is 76%. Overall survival is 97% and 100%, respectively.

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

Early results demonstrate that NOVP followed by radiation therapy is extremely well tolerated in patients with stage I-IIIA Hodgkin's disease. These results also appear to be similar to those expected for patients receiving NOVP and radiotherapy, even for patients with large mediastinal involvement 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 thrombopoiesis. IL-3, a second generation growth factor that acts on other hematopoietic progenitors, ameliorates both granulopoiesis and thrombopoiesis, 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 dose high dose therapy or mobilizing circulating hematopoietic stem cells is not yet established. Almost certainly a combination will prove most effective. 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 will be a reality within a decade. While the ability to change growth factors, is 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.

PHASE I/II DOSE-FINDING STUDY OF INTERLEUKIN-3 IN RELAPSED LYMOPHOMAS TREATED WITH IV CHEMOTHERAPY


Patients with malignant lymphomas (17 Non Hodgkin lymphomas – NHL, 11 Hodgkin’s disease – HD) resistant to previous rescue chemotherapy (cT3, n=23) or in first relapse (cT2, n=10). The IV IL-3 (lifostaside 2.5 g/m² q 3 days, etoposide 50 mg/m² q 1 day, etoposide 100 mg/m² q 1 day) was given at various doses (2.5, 5, 10.0 and 15.0 g/m²/kg) and schedules (5 or 10 days). All patients were pretreated (2-3 different regimens, 16 with additional radiotherapy) and in advanced stage. A total number of 69 courses (2-3 per patient) was given. Neutrophil- and platelet recovery was noted in pts receiving 10-15g/kg IL-3 as compared to lower doses. The median duration of neutropenia (ANC < 1.0 x 10⁹/l) was 6-14 days with absence of neutropenia in patients receiving the highest IL-3 dose (15 g/kg b.w.). The median number of thrombocytopenia (platelet count < 50x10⁹/l) was 3-5 ± 7 days with absence of thrombocytopenia in patients receiving 10-15 g/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 occurred only once (WHO grade 3). Adverse events associated with IL-3 were fever (n=18), dyspnoea (n=3), chills (n=5), local cutaneous reactions (n=4), transient parcellar effusion (n=2), headache (n=4) and transient tachycardia (n=2). Response was evaluable in 25 pts (NH1: 3 CR, 6 PR, 6 NC; HD: 5 CR, 5 PR) with durations up to 4 years so far. Circulating progenitor cells were transiently elevated up to 1000 fold. Cytokine levels were measured in serum and venous blood (GM-CSF and TPA): 3 cases showed transient increases of IL-6 associated with IL-3 administration. Statistically, elevated levels of GM-CSF were associated with duration of neutropenia, higher temperatures and occurrence of adverse events. IL-3 was well tolerated and effective in patients with resistant lymphomas.

INTERLEUKIN-3 (IL-3) IN VIVO: KINETIC OF RESPONSE OF TARGET CELLS. N. Aglietta M., Clinica Ospedale Maggiore, 26100 Novara, ITALY.

IL-3, human (Sandoz AG, Basel) was administered for 7 days to neoplastic patients with solid (cell) tumors. The 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 hematopoietic 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, lymphocytes and monocytes was observed. A mild monocytopenia and basophilia occurred. Eosinopenia, 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 response. Both the megakaryocyte progenitors (CFU-MK) and the granulocyte progenitors (CFU-GM) were the most sensitive. The IL-3 effect was present in the presence of G-CSF (granulocyte colonies), IL-5 (erythropoietin), 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, optimal response of myelopoiesis will require either endogenous or exogenous late acting cytokines such as G-CSF, Erythropoietin, GM-CSF. The effect of IL-3 on BM progenitors 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.

HUMAN RECOMBINANT INTERLEUKIN-3 (IL-3) AFTER AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) FOR MALIGNANT LYMPHOMA. W. F. Böhm, A. Rehmann, L. V. C. Raramon, H. C. Schotten, G. Venz, R. P., H. A. J. A. L. V. 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, n=16) and NHL with subsequent remission received ABMT after conditioning with BCNU, Etoposide, Ara-C, Cyclophosphamide (NH1) or Cyclophosphamide, BCNU, Etoposide (NH2). Prior to ABMT, one administration of IL-3 was given. Patients received IL-3 by continuous infusion for 14 days at doses ranging from 0.25 to 0.6 (n=5), 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 giving the data from 16 patients who completed IL3-treatment (8 males, 6 females, NH1 n=5, HD n=9, median age 32 years, range 16-58), were evaluated. All patients engrafted. The median time to reach a neutrophil count of 0.5 x 10⁹/l or a platelet count > 50 x 10⁹/l was 22 days (range 11-28) and 23 days (range 15-35) respectively for 6 patients treated with 10 µg IL-3 versus 27 days (range 13-40) and 30 days (range 11-40) for 10 patients receiving no or 0.25 µg IL-3. For the IL-3 (10 µg/kg) treated patients the median time to reach 1 x 10⁹/l neutrophils was 22 days (range 14-40) versus 40 days (range 21-40) for those receiving no or 0.25 µg IL-3. Side effects of IL-3 (n=6 patients) included facial flushing (5/6), headache (8/6) and fever (WHO grade 2 and 3) that required discontinuation in 1/6 and 3/6 patients treated with a dose of 10 µg and 15 µg respectively in patients with grade 3 fever circulating IL6 levels were significantly higher (> 1000 U/ml) then in patients without fever (< 20 U/ml) or with grade 1 fever (40 U/ml). These preliminary data indicate that IL-3 is a possible agent to stimulate 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 dose limiting. A total number of 34 patients with IL-3 and 38 patients will be presented. A phase III study is ongoing to further evaluate the efficacy of IL-3 in the setting of ABMT.
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MOBILISATION OF PERIPHERAL BLOOD AND EX VIVO EXPANSION OF HAEMOPOIETIC CELLS WITH CYTOKINES. C.A. Jumers, L.B. To, D.N. Haylock, P.G. Dymon, J. Rayly, C. Rawling, P.J. Simmons. Hanson Centre for Cancer Research and Royal Adelaide Hospital, Adelaide, South Australia.

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

Initial mobilisation techniques used the recovery period from myeloablatative 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 myeloablatative 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 haematopoietic 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 5-7 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.J. Missen, 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, espc. 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 G-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, 3 prospective studies have sufficiently matured to be discussed.

Two American studies were recently published (Ann Oncol 4: 205, 1993 and NEJM 327: 1393, 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 which 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.

α-INTERFERON FOR THE TREATMENT OF MULTIPLE MYELOMA. R. Herrmann. Division of Oncology, Department of Medicine, Kantonsspital (University hospital), 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 treatments 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 the 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-negative metaphases) was observed in 16% of IFN-treated patients vs 1% of chemotherapy treated ones after 8 weeks, 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 CML treated ones. Median survival was not yet reached by the former group after 60 months of treatment, while it was 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 achieved 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


Application of hematopoietic growth factors in hematopoiesis. 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-1a/BCI); 5) 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 has been 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 increases the number of circulating stem and progenitor cells. As compared with autologous marrow transplantation, accelerated stem cell mobilization has been observed when G-CSF or GM-CSF mobilized peripheral blood stem cells were reinfused after ablative treatment. (The presentation will be in German)
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