SATELLITE SYMPOSIA

SATELLITE SYMPOSIUM

CLINICAL EVALUATION OF NOVANTRONE IN LYMPHOMA THERAPY

WEDNESDAY, JUNE 6, 1990

ROOM A – 8:30-11:30 a.m.

MITOXANTRONE: AN ACTIVE AGENT IN REFRACTORY NON-HODGKIN'S LYMPHOMA

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A phase II-oriented study with Mitoxantrone was undertaken in 31 patients with refractory non-Hodgkin's lymphoma. The drug was administered through a 30-minute intravenous infusion at the dose of 14 mg/m² every three weeks. A minimum of two cycles were required to define treatment response. Twenty patients were previously treated with Adriamycin whose total dose was not exceeding 300 mg/m². Complete responses (CR) were documented in nine patients, and partial responses (PR) in five, for a total response rate of 47% (14 of 30). Of 20 patients previously treated with Adriamycin, CR occurred in five and PR in two. The median time to progression was three months. Mitoxantrone was well tolerated, and no patient refused treatment. Mild leukopenia was evident in 10 patients and thrombocytopenia in five. In all cases, electrocardiograms were obtained before each treatment cycle. Systolic time intervals and left ventricular ejection fraction were repeated after three cycles and at the end of therapy. Laboratory tests failed to document any major cardiac abnormality. Mitoxantrone is an effective agent in refractory non-Hodgkin's lymphoma and should be taken into consideration in the design of salvage regimens.

PHASE III COMPARATIVE TRIAL OF ADRIAMYCIN vs MITOXANTRONE (m-BACOD vs m-ENCOD) IN STAGE II-IV INTERMEDIATE- OR HIGH-GRADE NON-HODGKIN'S LYMPHOMA

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From September 1984 to July 1986, 70 untreated patients (pts) with intermediate- or high-grade non-Hodgkin's lymphoma (NHL), according to the Kiel classification, were enrolled in a phase III comparative study with the objective of comparing the efficacy and safety of Mitoxantrone (10 mg/m²) versus Adriamycin (45 mg/m²) in the combination regimen m-BACOD. Eligibility criteria were: stage > 1; performance status < 3; left ventricular ejection fraction (LVEF) > 50%, hepatic and renal functions normal. Patients were randomly assigned to either m-B-Adr-COD or m-B-Nov-COD for a total of 10 cycles and then were carefully restaged. Patients' characteristics, including sex, age, histology, symptoms, bulky disease, LDH values and performance status were balanced in the two groups. 67 pts were evaluable. Remission rate was 57% in both groups. At a median follow-up of 4 years, no significant difference was recorded regarding overall survival and relapse-free survival. Patients treated with Adriamycin had a higher incidence of alopecia ($P < 0.001$), nausea and vomiting, and presented a slightly greater mean drop of LVEF at the end of the treatment. Haematological toxicity was roughly similar in both groups. This trial indicates that a Mitoxantrone-containing regimen has equivalent efficacy but reduced clinical and cardiac toxicity compared with an Adriamycin-containing regimen in the treatment of intermediate- or high-grade diffuse NHL.

MITOXANTRONE IN PATIENTS WITH NEWLY DIAGNOSED LOW-GRADE NON-HODGKIN'S LYMPHOMA : HIGH ACTIVITY OF A DAILY SCHEDULE

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Twenty-one consecutive previously untreated patients with low-grade non-Hodgkin's lymphoma were entered into a trial of Mitoxantrone 5 mg/m² daily for 3 days q 3 weeks between 1985 and 1986. A cumulative dose of 165 mg/m² was not exceeded. Seven patients had small lymphocytic lymphomas, 10 patients had follicular small cleaved cell lymphomas and 4 patients had follicular, mixed small and large cell lymphomas (International Working Formulation). All 21 patients were evaluable for response and toxicity. 20/21 obtained remission, 9 CR and 12 PR. Non-hematologic toxicity was modest. No alopecia was seen and only 4 patients had nausea and vomiting (WHO grade 1-2). No cardiac toxicity was seen. White blood cell count on Day 12 was median 2.0×10^9/l (range $0.7\text{-}3.4 \times 10^9$/l). Platelet counts below 100×10^9/l were observed only in 5 patients. Cumulative toxicity which required dose reduction was observed in 13/18 patients (72%) and, in 6 patients, delay of treatment was necessary.

At the last analysis in 1988, with a median follow-up of 30 months, 7/20 patients had relapsed, and relapse-free survival totalled around 60%. An updated analysis of the study will be presented, including data on sequential studies of cardiac ejection fraction. (Previously published results : Cancer Chemother Pharmacol 1988; 22: 77-9).

SEQUENTIAL STUDIES ON THE ROLE OF MITOXANTRONE, HIGH-DOSE CYTARABINE AND RECOMBINANT HUMAN GRANULOCYTE-MACROPHAGE COLONY STIMULATING FACTOR IN THE TREATMENT OF REFRACTORY NON-HODGKIN'S LYMPHOMA

Ho AD, Del Valle F, Engelhard M, Hiddemann W, Rückle H Schlimok G, Haas R, Thiel E, Andreesen R, Fiedler W, Frisch J, Schulz G, Dörken B, Hunstein W

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Mitoxantrone (Novantrone, NO) and high-dose cytarabine (Ara-C, AC) have each been shown to be active in non-Hodgkin's lymphoma (NHL). The studies reported here are sequential. The first study (NOAC I) combined high-dose cytarabine (3 g/m² as 3h infusion weekly, 12h on Day 1) and Mitoxantrone (10 mg/m²/day on Days 2 and 3). Of 31 patients with relapsed and refractory NHL, 7 achieved CR and 7 PR. The median time to relapse of patients achieving CR was 7 months (4 - 17 months). Myelosuppression was the major toxicity of this regimen. Side effects were mild and included nausea and stomatitis. In the second study (NOAC II, cytarabine was escalated to 3 g/m²/12 h on Days 1 and 2 (4 doses) while Mitoxantrone remained 10 mg/m²/day on Days 2 and 3. The effects of recombinant human GM-CSF were simultaneously studied in some of the 9 participating centers.

Twenty-three patients from 5 centers were treated with NOAC II + rhGM-CSF while 14 patients from 4 centers received NOAC II alone. A complete remission was achieved in 9/23 patients who received rhGM-CSF in addition and in 2/14 patients treated with NOAC II alone. With rhGM-CSF the median duration of severe neutropenia (< 0.5/nl) after chemotherapy was 8 days vs a median of 13 days without rhGM-CSF. The duration of severe thrombocytopenia (< 20.0/nl) was not significantly different. The rates of infection and stomatitis were 25% and 17% respectively with rhGM-CSF compared to 53% and 60% without rhGM-CSF.

Thus, this last non-randomized pilot study indicates that administration of rhGM-CSF reduces the duration of chemotherapy-induced cytopenia and the rate of stomatitis. Moreover, this growth factor does not appear to result in stimulation and there was no suggestion of adverse effects on response rates or survival. We are currently conducting a controlled, randomized trial using NOAC II with rhGM-CSF or placebo to establish the definitive role of this growth factor in the treatment of NHL.

TREATMENT OF LOW-GRADE NON-HODGKIN'S LYMPHOMA BY CYTOREDUCTIVE CHEMOTHERAPY WITH PREDNIMUSTINE/MITOXANTRONE FOLLOWED BY INTERFERON ALPHA-2b MAINTENANCE: RESULTS OF A CLINICAL PHASE-II STUDY

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In a clinical phase-II study, the antilymphoma activity of the recently introduced combination of prednimustine and mitoxantrone (PmM) was evaluated in 17 patients with advanced low-grade non-Hodgkin's lymphoma after failure with or relapse after standard chemotherapy. The PmM regimen consisted of prednimustine 100 mg/m^2/day orally on days 1 - 5 and mitoxantrone 8 mg/m^2/day i.v. on days 1 and 2, which was repeated every 4 - 6 weeks to a maximum of six cycles. Patients achieving a complete or partial remission (CR or PR) received 2 additional courses for consolidation, followed by interferon (IFN) alpha-2b 5 x 10^6 units s.c. three times weekly until progression or relapse. Twelve of the 17 patients (71%) responded (4 CR, 8 PR). Side-effects with PmM consisted mainly of neutropenia, requiring reduction of dose in 48% of the treatment cycles. All 12 responding patients subsequently received IFN alpha-2b maintenance treatment. At present, remission duration ranges from 4.5+ - 17.5+ months with a median of 14.5 months. In comparison to unmaintained first remissions preceding this PmM/IFN trial, a clear tendency towards a longer period of freedom from progression was apparent in the 12 patients receiving IFN maintenance treatment during their second PR or CR.

These data provided the basis of a currently ongoing randomized multicentre study comparing initial chemotherapy with PmM *vs* COP (Cyclophosphamide, Oncovin, Prednisone) followed by a second randomization in CR and PR patients for maintenance therapy with IFN alpha-2b *vs* observation only.

PHASE II STUDY OF CCNU, ARA-C, MITOXANTRONE, PREDNISONE (CAMP): COMBINATION CHEMOTHERAPY FOR ADRIAMYCIN-RESISTANT INTERMEDIATE- AND HIGH-GRADE MALIGNANT NON-HODGKIN'S LYMPHOMA

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We conducted a phase II study to evaluate the efficacy and toxicity of CAMP chemotherapy (CCNU, ARA-C, Mitoxantrone and Prednisone) in Adriamycin-resistant intermediate- and high-grade malignant non-Hodgkin's lymphoma (NHL) in 31 patients. Inclusion and exclusion criteria are given. The complete remission rate was 25% and of relatively long duration (10, 16, 22, 23+, 30+, 35+, 39+, 43+ months). The partial remission rate was 23% and of short duration. The median survival time for complete responders was > 15 months. The median survival time for partial responders was only 5 months. Patient characteristics including age, sex, histology and bulky disease are given. The best responses were seen in patients with relapsed NHL in contrast to refractory disease, and in those with low tumor burden in contrast to bulky disease. The toxicity was mainly related to myelosuppression. This combination chemotherapy can be administered through the outpatients department. In conclusion, this report indicates the favourable efficacy and low toxicity of CAMP chemotherapy in patients with refractory or recurrent Adriamycin-resistant NHL of intermediate- and high-grade malignancy. CAMP chemotherapy warrants further clinical trials.

RECENT TRENDS IN THE MANAGEMENT OF LYMPHOMAS AT M.D. ANDERSON CANCER CENTER (MDACC)

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The overall therapeutic strategy for lymphomas at MDACC comprises new drug combinations which are tested first in relapsed cases and, if successful, incorporated into front-line management. In view of the effectiveness of two previous salvage regimens (SR) based on ifosfamide/VP-16 (IFX-VP-16) and Ara-C/Platinum (AP), a new SR (MINE-ESAP) was tested. MINE (Mesna 1.33 g/m^2 i.v. mixed with IFX 1.33 g/m^2/d x 3, Novantrone 8 mg/m^2 x 1, Etoposide 65 mg/m^2/d x 3 plus Mesna 500 mg p.o. 4 h after each IFX dose) is given to maximum response, and followed by consolidation with 3-6 courses of ESAP (ASCO 1989; 8:256). Results comparing MINE-ESAP to prior IFX-VP-16 ('MIME') and AP ('ESAP') regimens are:

Salvage regimen	N	CR+PR (%)	12 mos FFS (%)	12 mos survivial (%)
MINE-ESAP	32	69	60	78
MIME	221	60	20	38
ESAP	101	58	31	57

These preliminary results are the best we have observed and strongly suggest the value of these 2 non-cross-resistant combinations. We have recently started testing an alternating triple-therapy (ATT) first-line regimen for MDA stages B, C, D intermediate-grade lymphomas. ASAP (Adriamycin, Solumedrol, Ara-C, Platinum) is delivered first and alternated with M-BACOS (Methotrexate, Bleomycin, Adriamycin, Cytoxan, Oncovin, Solumedrol), then MINE for a total of 9 courses. A statistically significant improvement in MDA Stage D (high tumor burden, high LDH) has been seen, but no differences so far in Stages B and C.

First-line regimen	Actuarial 1-year FFS in MDA Stage B	Stage C	Stage D
ATT	85% (N=14)	62% (N=23)	60% (N=12)
CHOP-Bleo	87% (N=86)	63% (N=76)	29% (N=38)

Finally, a new and intensive therapeutic strategy with curative intent has been devised for stages III and IV low-grade lymphoma involving rotation of CHOP-Bleo, ESAP and NOPP (Novantrone, Oncovin, Procarbazine, Prednisone). Maintenance interferon is given once yearly. It is too early to assess results so far.

NOVP (NOVANTRONE, VINCRISTINE, VINBLASTINE, PREDNISONE), A NOVEL CHEMOTHERAPEUTIC REGIMEN: ADJUVANT THERAPY FOR STAGES IA-IIIB HODGKIN'S DISEASE

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We have previously identified adverse prognostic factors for patients (pts) with stages I-II Hodgkin's disease (HD) treated with irradiation (XRT) alone. These included hilar adenopathy, mediastinal masses 7.5 cm or greater in diameter on a posterior-anterior chest x-ray and B symptoms. When such pts were treated with 2 cycles of MOPP (Mustargen, Oncovin, Procarbazine, Prednisone) prior to XRT, disease-free survival rates were better: 87% are expected to be alive with no recurrences at 5 years. Pts with stage III disease also have improved disease-free survival rates with combined modality therapy compared with those seen following XRT alone. For those with stage IIIA, III$_1$B or III$_2$B (without pelvic disease), disease-free results at 10 years are 84% when treated with only 2 cycles of MOPP prior to XRT. However, MOPP is associated with potential significant toxicity, including nausea and vomiting, sterility, neutropenic infection and secondary leukemia. For this reason, we designed NOVP (Novantrone 10 mg/m^2 Day 1, Vincristine 2 mg Day 8, Vinblastine 6 mg/m^2 Day 1, Prednisone 100 mg Days 1-5 q 3 weeks) to treat pts with clinical (CS) or pathologic (PS) stage I-III$_2$B disease. Each patient receives 3 cycles of NOVP followed by XRT: the mantle and upper abdomen for CS I-II and PS III; the mantle and abdominal spade for III$_2$; the mantle, abdomen and pelvis for III$_3$A (with pelvic disease). We have treated 27 evaluable pts with a median follow-up of 12 months. With NOVP alone, 12 (44%) achieved complete remission (CR), 14 (52%) partial remission, and one failed. All pts with responding disease (RD) completed XRT as planned. Of the 26 RD pts, one with lower torso stage IIA disease has had relapse in a cervical node and was treated with the mantle to CR. The one failure with NOVP did not respond to MOPP or ABDIC (Adriamycin, Bleomycin, DTIC, CCNU, Prednisone), but is currently in CR following bone marrow transplantation. Toxicity has been minimal with no cardiopulmonary toxicity, no significant alopecia, no permanent azoospermia and little nausea. We conclude that NOVP provides excellent cytoreduction prior to definitive XRT for stages I-III$_2$B HD. These results are very encouraging; longer follow-up may determine if disease-free survivals are as good as those obtained after MOPP and XRT.

SATELLITE SYMPOSIUM

NEW ASPECTS OF INTERFERON THERAPY IN HAEMATOLOGICAL MALIGNANCIES AND LYMPHOMAS

WEDNESDAY, JUNE 6, 1990

ROOM B – 11:30-15:30 p.m.

CHRONIC MYELOGENOUS LEUKEMIA: OVERVIEW OF MOLECULAR MECHANISMS AND INTERFERON-ALPHA THERAPY.

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Chronic myelogenous leukemia is a clonal myeloproliferative disorder which displays several cardinal features: (i) a progressive course from a chronic phase to a blast transformation phase; (ii) a cytogenetic marker, the Ph chromosome (t(9;22)(q34;q11)); and (iii) consistent molecular abnormalities including the disruption of the BCR and ABL genes on chromosome 22 and 9 respectively, and their subsequent juxtaposition in a configuration resulting in an aberrant BCR-ABL gene encoding an enzymatically-altered BCR-ABL protein ($p210^{BCR-ABL}$).

Recently, we have shown that newly-diagnosed CML patients will respond to interferon-alpha therapy. Approximately 70% of these individuals achieve a complete hematologic response; about 15%, a complete cytogenetic response. In contrast, patients with a chronic phase duration of over one year have a low rate of hematologic response (25%) and rarely achieve cytogenetic remission. Currently, our laboratory is analyzing molecular mechanisms of response and resistance to interferon-alpha, and the pathogenesis of disease progression. We will present data demonstrating that a) resistance to interferon-alpha is probably not caused by defective induction of interferon-stimulated genes; b) multiple molecular pathways of disease progression probably exist and may include additional alterations in BCR-ABL products and aberrant growth factor (interleukin-1B) production; and c) the events driving disease progression may also be important in the mediation of resistance to interferon therapy.

AN UPDATE OF THE ITALIAN MULTICENTRE STUDY OF ROFERON-A VERSUS CONVENTIONAL CHEMOTHERAPY IN CHRONIC MYELOID LEUKEMIA.

M. Baccarani, D. Russo, E. Zuffa and M. Fiacchini (Interim Report Committee for the Italian Coop. Study Group on CML), Chair of Hematology, University of Udine, and Institute of Hematology "L. and A. Seràgnoli", University of Bologna, Italy.

A number of studies have already provided evidence that human recombinant α-IFN is effective for treatment of chronic myeloid leukemia (CML) and have raised interest and hope because treatment can lead to a selective elimination of leukemic cells, resulting not only in hematologic remissions but also in cytogenetic ones. In order to assess the frequency, the features and the duration of α-IFN induced and maintained hematologic and cytogenetic remission, as well as the effect of chronic α-IFN treatment on the duration of chronic phase and survival, the Italian Coop. Study Group on CML undertook a prospective randomized trial of ROFERON-A (ROF-A) vs. conventional chemotherapy (CHT). All patients with Ph+ CML who were first seen at 46 collaborating Hospitals between June 1986 and June 1988 were enrolled, up to a total of 346 cases, providing a power 0.90 with a probability 0.05 of detecting a 0.20 difference in survival between ROF-A and CHT arm. Treatment by ROF-A consisted of 9 MU daily for the first 8 mo., with subsequent escalation in the case of partial or no response. CHT consisted of Hidroxyurea (HU). Hematologic response after 3,8, and 14 mo. was identical, but 18% of patients in ROF-A arm requested also HU for quantitative disease control. Cytogenetic responses at 8 and 14 mo. were 44 and 47% in ROF-A arm vs. 20 and 21% in CHT arm. However 30% of ROF-A induced cytogenetic responses were substantial (i.e. 75 to 100% metaphases were Ph-), while in CHT arm all cytogenetic responses were insignificant (i.e. only 2 to 20% metaphases were Ph-). The probability of getting any cytogenetic responses was significantly related with the maximum tolerated dose of ROF-A. The probability of getting any hematologic and cytogenetic responses including substantial cytogenetic ones, was significantly related with the relative risk, that was calculated according to Sokal et al (Blood, 1984): low-risk (<0.8) patients were more responsive to ROF-A than high-risk ones (<1.2). A preliminary analysis of the data collected after 24 mo. of treatment will be presented and discussed at the Symposium.

Supported by AIRC.

INTERFERON ALPHA COMBINATION THERAPY IN MULTIPLE MYELOMA.

Håkan Mellstedt, Department of Oncology (Radiumhemmet), Karolinska Hospital, Stockholm, Sweden, for The Myeloma Group of Central Sweden (MGCS).

MGCS members: M. Björkholm, M. Björeman, G. Brenning, G. Gahrton, G. Grimfors, H. Gyllenhammar, R. Hast, B. Johansson, G. Juliusson, M. Järnmark, A. Killander, E. Kimby, R. Lerner, C. Paul, B. Simonsson, B. Smedmyr, A-M. Stalfelt, H. Strander, E. Svedmyr, A-M. Udén, B. Wadman, E. Ösby. Dept. of Oncol., Dept. of Med., Karolinska Hospital, Dept. of Med., Danderyd Hospital, Dept. of Med., South Hospital, Dept. of Med., Huddinge Hospital, Stockholm, Dept. of Med., Akademic Hospital, Uppsala, Dept. of Med., Örebro Hospital, Örebro.

α-interferon (α-IFN) is a biologic therapeutic with documented antitumoral effect in multiple myeloma. In previously treated patients the response frequency to α-IFN alone was 17% (95% conf. lim. 12-22%) and in newly diagnosed patients 34% (95% conf. lim. 27-41%).

The mechanisms of action are not clear but a lot of functions might be operating. A dose-dependent direct cytotoxic effect has been shown in vitro which is probably also the case in vivo. A synergistic inhibitory effect on myeloma cell colony formation in vitro has been shown between α-IFN and melphalan/prednison (PM). Moreover, α-IFN might also act by inhibiting the growth promoting effect of IL-6, by an increase of NK cell functions, by expansion of cytotoxic T cells and by increase of relevant surface antigenic structures.

With the aim to study the therapeutic synergy between α-IFN and MP a randomized study was started in April 1986. All newly diagnosed patients with clinical stage II and III were entered. One group (MP) received MP therapy every 6th week. The other group (MP/IFN) was given MP every 6th week and natural α-IFN (Finnferon, Finnish Red Cross, Helsinki, Finland) 7 x 10^6U/m^2/day x V s.c. every 3rd week. When a response was achieved the α-IFN was reduced to 3 x 10^6U/day 3 days a week continuously. MP was continued every 6th week.

220 patients have entered the study. The response frequency was 48% in the MP group and 66% in the MP/IFN group (p=0.02). Stage II patients responded better to MP/IFN (76%) than to MP (48%)(p=0.01). No significant difference was noted for stage III patients. 91% of all IgA myelomas responded to MP/IFN while 52% responded to MP (p=0.01). The difference in response frequency of IgG and BJ myeloma between the two treatment groups was statistically not significant. So far, the difference in response duration and in overall survival between the two treatment groups is statistically not significant. However, the statistically significant increase in survival for MP/IFN patients in stage II and for MP/IFN patients ≤ 65 years of age compared to MP patients was found.

MAINTENANCE OF REMISSION WITH HUMAN RECOMBINANT ALPHA-2 INTERFERON (ROFERON-A) IN PATIENTS WITH STAGES III AND IV LOW GRADE MALIGNANT NON-HODGKIN'S LYMPHOMA.

A. Hagenbeek and J.H. Meerwaldt on behalf of the EORTC Lymphoma Cooperative Group. The Dr. Daniel den Hoed Cancer Center, P.O. Box 5201, 3008 AE Rotterdam, The Netherlands.

The majority of patients with stages III and IV non-Hodgkin's Lymphoma (NHL) of low grade malignancy will ultimately die from the disease, with median survival times of 6 to 10 years from diagnosis. Although most patients respond well to a variety of treatments, be it single drugs or combination chemotherapy, none of the current therapies induce prolonged relapse-free survival in the majority of patients. Obviously, there is a need for continued clinical trials that seek curative therapies.

Recent phase II studies have indicated that alpha-2 interferon (IFN) has significant effects in NHL of low grade malignancy. Based on this finding and the fact that IFN seems especially active in the stage of "minimal residual disease" a prospective, randomised phase III study was initiated 3½ years ago in the EORTC Lymphoma Cooperative Group. The objective of the study is to investigate whether prolonged interferon administration in the phase of "minimal residual disease" will increase relapse-free survival or postpone progression of disease.

Previously untreated patients older than 15 years with NHL of low grade malignancy (Working Formulation class B, C, D) are eligible. All patients receive 8 courses of combination chemotherapy (Cyclophosphamide 300 mg/m^2 per os, days 1-5; Vincristin 1.4 mg/m^2 i.v. day 1, maximally 2.0 mg, and Prednisone 40 mg/m^2 per os per day, days 1-5). Courses are given every three weeks. After 8 courses of CVP all patients are being evaluated. Those who show progressive disease go off study. All other patients (complete remission, partial remission, no change) are submitted to iceberg radiotherapy according to conventional guidelines. Thereafter, they are randomised to either recombinant alpha-2 interferon (Roferon-A) 3x10^6 IU s.c. three times per week for a period of 12 months or to "no further treatment".

As of October 1989, 209 patients have been enrolled, of which 93 are still in the chemo-radiotherapy induction phase. So far, 116 patients have been randomised (56 IFN; 60 "no further treatment"). After 8 courses of CVP the total response rate was 86% (56/122 = 46% complete remission, CR, and 48/122 = 40% partial remission, PR); 18/122 (14%) of the patients had no change or progressive disease. In 38% of patients who received iceberg radiotherapy in PR a CR was achieved. So far, overall survival for all patients is 84% at 30 months; disease-free survival at 30 months is 36%. Obviously, as the study still runs, possible differences between both arms are not to be disclosed at this moment.

INTERFERON α-2a IN CUTANEOUS T-CELL LYMPHOMA. G. Papa*, M.L. Vegna°, D. Defazio°, G. Coppola**, O. De Pità**, P.Puddu**, G. Ferranti**, R. Simoni**, D. Criscuolo°°, F. Mandelli°. *Cattedra di Ematologia, II Università, Rome, Italy °Cattedra di Ematologia, Università "La Sapienza", Rome, Italy **Istituto Dermopatico dell'Immacolata, Rome, Italy °°Clinical Research, Roche, Milan, Italy.

The study was designed to evaluate the therapeutic efficacy and the toxicity of α-2a recombinant interferon (Roferon A, kindly provided by Hoffman-La Roche) given as initial systemic therapy in mycosis fungoides and/or Sèzary syndrome patients, not previously exposed to either cytotoxic or estensive radiation therapy, at a slowly escalating schedule to the maximal tolerated dose than could be given without debilitating side effects. Between february 1986 and june 1987, 23 newly diagnosed patients with cutaneous T-cell lymphoma were treated with sub-cutaneous recombinant leukocyte interferon α-2a (IFN). IFN was administered daily with dose escalation from 3 to 18 million units for 12 weeks; thereafter patients induced into complete (CR) or partial (PR) remission were given IFN at maximal tolerated dose 3 times weekly for 6 or 9 months. There were 18 males and 5 females with a median age of 55.6 years (range: 20-70 yrs). 12 patients had plaque lesions, 5 had generalized erythroderma, 4 of these had circulating Sèzary cells. No patient had visceral disease on abdominal CT scan and/or sonorogram. All patients were untreated, but one who had received topical skin irradiation. All patients completed induction phase and are evaluable for response to therapy. The objective tumor response was observed in 17 pts (74%): 8 (35%) were CR and 9 (39%) were PR. Median time to achieve the response was 5 months (range: 3-9 months). Two had a stable disease and 3 progressed during induction. A 74 years old patient died because of neutropenia and sepsis at the end of induction, while receiving IFN at dose of 18 MU. Disease stage is the pretreatment feature predictive of response to IFN therapy. In IA, IB and IIB stages the response rate was 100%, 83% and 80%, respectively. In stage IVA the response rate was 57%; in this stage only one CR was achieved. All patients experienced a flu-like syndrome at the onset of the treatment; however only in very few cases dose reductions was required because of this side effects. Liver toxicity, fatigue and leukopenia accounted for 80% of dose modifications requests. All patients recovered uneventful from these side effects, but a 74 years old patient, who died of neutropenia effect. Two out of 8 CR patients have relapsed after 18 and 24 months from response; the remaining 6 patients are in continuing CR with a median follow-up of 41.8 months (range: 36.6 - 43.1) Among the 9 PR patients, 6 have progressed from 8 to 17 months after response. In the 3 PR patients not yet progressed the response duration ranges from 20 to 24 months. The actuarial duration of continuous complete remission projected the 52% of 17 responding patients at 43 months; while the actuarial event-free survival projected the 38% of all patients at 48 months. In conclusion IFN α-2a is a very effective as a single agent in untreated cutaneous T-cell lymphomas with an overall response rate of 74%. The dose schedule of this study was generally well tolerated: most of the patients remained ambulatory, continuing their normal activity. The evidence that most of the patients (7/8) achieved CR after 6 months during treatment suggests to consider a longer induction phase. A lower dose or a less step dose escalation may be necessary in older patients to decrease the risk of fatal infections. An association of IFN with other antitumor agents may be necessary in more advanced disease.

EARLY RESULTS OF ALPHA 2A INTERFERON (ROFERON) TREATMENT OF CHRONIC LYMPHOCYTIC LEUKAEMIA. F.J. Giles,[1] C.P. Worman,[1] R.A. Gaffar[1], A. Jewell,[1] J.C. Cawley,[2] D. Galvani,[2] T.R. Grant[3], A.V. Hoffbrand[4], A.B. Mehta[4], A.C. Newland[5], A.H. Goldstone[1]. Departments of Haematology, University College Hospital, London WC1,[1] Royal Liverpool Hospital, Liverpool L69 3BX[2], Barking Hospital, Essex,[3] Royal Free Hospital School of Medicine London NW3[4], London Hospital, Whitechapel, London E1[5].

Twenty patients have now entered a multicentre study to assess the efficacy of recombinant alpha 2a interferon in the prevention of progression of early stage chronic B lymphocytic leukaemia (B-CLL). The study regimen is 3MU alpha 2a interferon self administered thrice weekly by subcutaneous injection. Currently available results are those of patients who have undergone more than 3 months therapy. Although rate of response varied between individuals, all patients showed an initial response of a 20-80% reduction in their lymphocytosis. Throughout individual treatment periods (3-17 months), although transient variations occurred, only two patients exhibited a net drop of Hb >1.5 g/dl, both after 17 months continuous interferon therapy. One patient had a marked net drop in both platelets and neutrophils following 12 months interferon therapy. 3 patients (2 at 6 months, 1 at 9 months) have some evidence of disease progression whilst on therapy. This has been indicated by a marked increase in peripheral CD5+ light chain restricted B cells in all 3 patients. The possible reasons for relapse are currently under investigation. One of these patients has now ceased alpha interferon therapy and to date minimal changes have occurred in the absolute values of non-B lymphocytes and the reduction of lymphocytosis confined to clonal B cell populations. Sequential in vitro stimulation assays involving pokeweed mitogen (PWM) have shown both an increase in ^{3}H-thymidine uptake and IgM/IgG secretion in the overall lymphocyte populations in patients on interferon therapy. Whilst it is obviously too early to draw firm conclusions on the possible long term benefits of recombinant alpha 2a interferon usage in early stage CLL it is clear that it can lead to an early reduction in lymphocytosis and in some patients a return towards normal lymphocyte cell function.

SATELLITE SYMPOSIUM

RECENT ADVANCES IN LYMPHOMA TREATMENT

WEDNESDAY, JUNE 6, 1990

ROOM A – 12:00-3:30 p.m.

CAN HODGKIN'S DISEASE BE SALVAGED? G.P. Canellos. Dana-Farber Cancer Institute, Boston, Massachusetts 02115

The availability of an increasing number of active agents has led to the development of a succession of regimens for use as alternative and second-line therapy following relapse from or refractoriness to MOPP or its variants. ABVD has been the most widely used and has been considered "non-cross-resistant." Other programs containing the nitrosourea CCNU have been used with results similar to ABVD. A relatively small fraction of relapsed patients remain failure free at 5 years (about 20% to 30%) despite a 30% to 60% second-line complete response (CR) rate. The few randomized trials (CALGB, EORTC) evaluable to assess the efficacy of alternating MOPP/ABVD compared to MOPP alone have shown a small but significant advantage in freedom from progression and/or survival, favoring the complex regimens over MOPP. The CALGB trial (8251) included a third arm of ABVD alone. The ABVD and MOPP-ABVD arms had a higher CR rate and superior failure-free survival (FFS) over MOPP, but have thus far shown no difference between ABVD and alternating MOPP/ABVD, suggesting that full doses of a single regimen are equivalent to the more complex multidrug regimen. The next step in the CALGB program was to attempt to improve ABVD. The substitution of VP-16, an active single agent, for DTIC and bleomycin in ABVD resulted in a new regimen, EVA. This program has already demonstrated a 66% response rate in MOPP-resistant/relapsed patients (CALGB 8751). The median FFS is about 10 months and closely resembles the FFS curve of ABVD used as a cross-over treatment for relapse/resistance in the MOPP alone arm in the CALGB trial mentioned above. The EVA program is without pulmonary toxicity and offers the potential for dose escalation of VP-16. Future trials could compare ABVD to EVA as primary therapy, especially if ABVD is equivalent to the hybrid in the current intergroup trial (CALGB 8952).

High-dose therapy with autologous bone marrow transplantation (ABMT) or stem cell support represents intensive salvage treatment for those who fail at least two regimens.. In 1989, 240 patients were reported with a CR rate of 46%, whereas 35% were continuously free of disease at 3 years. The criteria that predict a good response are as follows: 0 performance status; sensitive relapse; and failure of up to two regimens. Longer follow-up is still required to determine the final effect of ABMT.

MACOP-B AND VACOP-B IN DIFFUSE LARGE CELL LYMPHOMAS AND MOPP/ABV IN HODGKIN'S DISEASE. S.E. O'Reilly, R. Fairey, P. Hoskins, R. Klasa, P. Klimo, N. Voss and J. Connors. B.C. Cancer Agency and the University of British Columbia, Vancouver, Canada, V5Z 4E6.

Between 1981 and 1986, 126 patients with diffuse large cell lymphomas were treated with MACOP-B (mixed, large cleaved, large noncleaved or immunoblastic). All had advanced stage (B symptoms, tumor >10 cm or Ann Arbor stage 3 or 4), age <71. Since June 1986, the MACOP-B regimen has been modified in the expectation of enhancing efficacy and reducing toxicity, particularly stomatitis. The new regimen VACOP-B is shown below.

DRUG:		WEEK 1	2	3	4	5	6	7	8	9	10	11	12
Etoposide	50 mg/m2 IV day 1			x				x				x	
	100 mg/m2 PO day 2,3			x				x				x	
Doxorubicin	50 mg/m2 IV	x		x		x		x		x		x	
Cyclophosphamide	350 mg/m2 IV	x				x				x			
Vincristine*	1.2 mg/m2 IV		x		x		x		x		x		x
Bleomycin**	10 U/m2 IV		x		x		x		x		x		x
Prednisone***	45 mg/m2 PO daily	x1 wk then every other day x 11 wk ****											
Cotrimoxazole	1 DS PO BID	- - - - - - - - - - - - - - -											
Ketoconazole	200 mg PO daily	x1 wk then every other day x 11 wk											
Cimetidine	600 mg PO BID	x1 wk then every other day x 11 wk											

* No maximum dose of vincristine. ** With 100 mg hydrocortisone. *** Round to nearest 25 mg. **** Continue to end of wk 14.

Cisplatin was added to the etoposide for 72 patients (50 mg/m² for 45, 30 mg/m² for 27) without evident impact on efficacy but definite increase in nausea, vomiting and anemia.

108 patients have been treated with VACOP-B.

Current results compared to MACOP-B are as follows.

			Toxic Deaths		Survival (Unadjusted)		FFS
	n	CR%	n	%	3 yr %	8 yr %	8 yr %
MACOP-B	126	84	8	6	67	62	52
VACOP-B	108	81	3	3	60		

After adjustment for prognostic variables (B symptoms, age >60, more than 1 extranodal site) the 3 yr actuarial overall survival is slightly, but not significantly, better after VACOP-B. Non-fatal toxicity was similar for the two regimens except that moderate or severe mucositis and Cushingoid changes were seen much less frequently during VACOP-B.

For MACOP-B, follow-up is 39-106 mo (med. 76 mo) for living pts, 71 pts are alive in 1st CR, 4 alive in 2nd CR, 3 alive with low grade relapse, 1 alive with large cell relapse, 4 unrelated deaths in CR, 7 toxic deaths and 36 deaths from lymphoma.

MOPP/ABV Hybrid chemotherapy for advanced stage Hodgkin's disease (HD) was standard therapy from April 1981 to June 1988 for untreated advanced stage HD patients aged 16-65.

Nitrogen Mustard	6 mg/m2 IV D1	Doxorubicin	35 mg/m2 IV D8
Vincristine*	1.4 mg/m2 IV D1	Bleomycin	10 mg/m2 IV D8
Procarbazine	100 mg/m2 PO D1-7	Vinblastine	6 mg/m2 IV D8
Prednisone	40 mg/m2 PO D1-14		

Repeat every 28 days *Maximum 2.0 mg

Patients with stages 2B, 3B, 4B, 3A, 4A or stages 2 or 3A with >5 splenic nodules all received a minimum of 8 cycles of chemotherapy. All other stages with a mediastinal mass >1/3 of the transthoracic diameter received 6 cycles of chemotherapy plus involved field radiotherapy, except patients with stage 1 or 2A nodular sclerosing HD with a mediastinum >1/3 - these received 3 cycles of chemotherapy and mantle radiotherapy.

Projected 7 yr overall survival (OS) and failure-free survival (FFS) - failure defined as primary progression, relapse or death from any cause:

Stage		n	OS	FFS
	2A	14	88	70
	2B	26	82	80
	3A	53	80	76
	3B	35	81	69
	4A	15	93	78
	4B	27	82	70
	ALL	170	77	62

	n	OS	FFS
Symptoms			
A	82	70	61
B	88	80	70
Mediastinum			
0	47	66	60
<1/3rd	69	89	78
>1/3rd	54	86	64

These results indicate that MOPP/ABV is a successful regimen for advanced Hodgkin's disease irrespective of stage, presence of B symptoms or bulky mediastinal disease.

The National Cancer Institute of Canada have just completed enrollment on a randomized study comparing MOPP/ABV with MOPP/ABVD in advanced stage or recurrent Hodgkin's disease, the results of this study are awaited.

MOPP/ABV has now been further modified to provide a potentially nonsterilizing and nonleukemogenic regimen for advanced stage Hodgkin's disease. This regimen, VECABOP, comprises vinblastine, etoposide, low dose cyclophosphamide, doxorubicin, bleomycin, vincristine and prednisone on a 21 day schedule.

55 patients have now been treated with VECABOP 48 of whom had advanced stage newly diagnosed HD and 7 had early stage HD. There have been 6 treatment failures in the 2 yrs this regimen has been studied. As yet, long-term results are not available, but acute toxicities such as nausea, vomiting and phlebitis have been significantly reduced. Longer follow-up will be needed for this experimental regimen.

ETOPOSIDE, IFOSFAMIDE, AND METHOTREXATE WITH OR WITHOUT BLEOMYCIN IN REFRACTORY OR RECURRENT LYMPHOMAS

Nowrousian M.R., Anders C., Niederle N., Nagel-Hiemke M., Moritz T., Seeber S., Schmidt C.G. West German Tumor Center, University of Essen, Department of Internal Medicine (Cancer Research), 4300 Essen, F.R.G.

Patients (pts) with refractory or relapsed malignant lymphomas are known to have a poor prognosis. To improve the results in these pts, we have used a therapeutic regimen consisting of etoposide (90 mg/m²/d, days 1,3,5), ifosfamide (1,200 mg/m²/d + mesna, days 1-5) and methotrexate (30 mg/m²/d, days 1,5) with or without bleomycin (15 mg/d, days 1,5,12) (VIMB). Forty-seven pts (32 males, 15 females), ranging in age from 17 to 66 years (median, 45), were treated. Of the 47 pts, 15 had relapsed following a complete response (CR) to first-line chemotherapy, 28 had failed to achieve CR to front-line therapy, and 4 had failed to respond to multiple salvage regimens given after relapses of their disease. All pts had received extensive prior chemotherapies, with combinations containing doxorubicin in 36 of 47 pts. Histologic types of lymphomas (Kiel classification) were lymphoblastic (3), immunoblastic (2), immunoblastic-centroblastic (1), centroblastic (11), undifferentiated large cell (9), pleomorphic T-cell (2), centrocytic (3), centrocytic-centroblastic (3), lymphoplasmocytoid (2), and Hodgkin's disease(11). The overall response rate was 87% with 45% CR and 42% partial responses (PR). The median relapse-free interval was 8 months in pts with CR and 6 months in those with PR. 43% of pts with CR were predicted to be without relapse at 2 years and 31% at 5 years. The median survival time for all pts treated was 14 months, for those with CR 22 months, and those with PR 10 months. The probability of survival at 2 years was 27% in all pts, 50% in pts with CR, and 15% in those with PR. On the basis of these results, VIMB appears to be effective in pts with refractory or recurrent lymphomas, resulting in response in a large number of pts, and long-term survival and possible cure in a small but significant number of pts.

RESULTS OF RECENT SALVAGE REGIMENS (SR) TESTED AT M.D. ANDERSON CANCER CENTER (MDACC). F. Cabanillas, M.A. Rodriguez, W.S. Velasquez, F. Swan, F.B. Hagemeister, P. McLaughlin, J.R. Redman, J.E. Romaguera. University of Texas M.D. Anderson Cancer Center, Houston, TX 77030

From 1981 to 1989, we explored 4 SR in 474 patients with recurrent lymphoma. The first SR consisted of MIME (methyl-GAG 500 mg/m² day 1, ifosfamide 1 g/m²/d x 5, methotrexate 30 mg/m² days 3 and 10, etoposide 100 mg/m² days 1-3). Subsequently, a totally different and synergistic combination based on Ara-C/platinum, DHAP (dexamethasone 40 mg intravenously [IV] x 4, high-dose Ara-C 2 g/m² x 2 q12h starting at the end of the platinum 100 mg/m² given as a 24-h infusion), was tested. Etoposide was later added to this regimen in the ESAP combination (etoposide 60 mg/m² x 4, methylprednisolone 500 mg IV x 4, high-dose Ara-C 2 g/m² x 1 at the end of a 96-h continuous infusion of platinum 100 mg/m²). In view of the effectiveness of the ifosfamide/etoposide- and Ara-C/platinum-based SR and because of their potential lack of cross resistance, a new strategy was devised in 1988. Treatment starts with MINE (mesna 1.33 g/m²/d IV x 3 + 500 mg PO 4 h after each ifosfamide dose of 1.33 g/m² x 3, Novantrone 8 mg/m² IV x 1, etoposide 65 mg/m² IV x 3) and is given to maximum response (in case of complete response [CR] = 6 courses). This is consolidated with 3 courses of ESAP (for CR on MINE) or with 6 for others. An additional 30 patients who had previously been exposed to Ara-C/platinum were given MINE without crossover to ESAP and constitute a separate subset. Results are shown below and compared with those of other SR.

Regimen	No.	CR + PR (%)	12-mo Failure-Free Survival (%)	12-mo Survival(%)
MINE-ESAP	32	69	60	78
MIME	221	60	20	38
DHAP	90	55	24	34
ESAP	101	58	31	57
MINE	30	40	4	11

These preliminary results obtained with the MINE-ESAP regimen are the best we have observed at 12 months of follow-up and suggest that the sequential use of these 2 non-cross-resistant combinations can improve the quality of the responses.

ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

LONG-TERM FOLLOW-UP OF ProMACE-CytaBOM IN NON-HODGKIN'S LYMPHOMAS. Richard I. Fisher, Dan L. Longo, Vincent T. DeVita, Jr, Thomas P. Miller, and Robert C. Young. National Cancer Institute, Bethesda, MD 20892 and Southwest Oncology Group, San Antonio, TX 78229

Initial results from studies using third-generation combination chemotherapy regimens for the treatment of aggressive non-Hodgkin's lymphomas demonstrated complete remission (CR) rates that were higher than those reported with first-generation regimens. Long-term follow-up of these studies is required to know if the increased number of CRs translates into greater numbers of long-term disease-free survivors. This report describes results obtained with one of the third-generation regimens, ProMACE (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide)-CytaBOM (cytarabine, bleomycin, vincristine, methotrexate).

From 1981 to 1988, 193 patients with stage II, III, or IV aggressive non-Hodgkin's lymphoma treated at the National Cancer Institute were randomly assigned to receive either ProMACE (day 1)-CytaBOM (day 8) or ProMACE (day 1)-MOPP (mustard, vincristine, procarbazine, prednisone) (day 8). The doses and schedule were previously published (Fisher et al: Proc ASCO 1984, Longo et al: Proc ASCO 1987). With a median follow-up of 5 years, the CR rate was 86% for ProMACE-CytaBOM v 74% for ProMACE-MOPP ($P = .048$). A plateau in the disease-free survival curve was seen at 69% for ProMACE-CytaBOM v 54% for ProMACE-MOPP ($P = .082$). A plateau was also seen in the overall survival curves at 69% for ProMACE-CytaBOM v 53% for ProMACE-MOPP ($P = .046$).

In 1985, the Southwest Oncology Group conducted a phase II study of ProMACE-CytaBOM in 78 patients with stages II to IV intermediate- or high-grade non-Hodgkin's lymphoma to determine the CR rate and long-term disease-free survival with this regimen in a national cooperative group setting. The CR rate was 57%. At median follow-up of 38 months, disease-free survival is 50% at 3 years, and overall survival is 57% at the same timepoint.

Ultimate conclusions concerning the efficacy of this regimen await results of the National High Priority Lymphoma Trial, which compares CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) v m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone) v ProMACE-CytaBOM v MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin).

THE PLACE OF THIRD GENERATION REGIMENS IN THE TREATMENT OF PATIENTS WITH LARGE CELL LYMPHOMA. James O. Armitage, M.D., University of Nebraska Medical Center, Omaha, NE.

Diffuse large cell lymphoma (DLCL), the most common form of aggressive non-Hodgkin lymphoma, has been known to be curable with combination chemotherapy for almost 20 years. Although occasional patients were cured with regimens like COP, the development of 4-drug regimens made cure possible in a significant percentage of patients. Subsequently, newer regimens (i.e. often referred to as "third-generation" regimens) incorporated even more drugs with an apparent increase in the cure rate. However, the identification of important clinical and biologic features in the patient or the tumor that predict for treatment outcome (i.e. prognostic factors) has complicated comparison between non-randomized and non-concurrent trials. Recently SWOG has presented data from pilot studies showing that patients treated with ProMACE/CytaBOM, m-BACOD and MACOD-B did not seem to do better than patients treated in the past with CHOP. Also, ECOG has presented a study in which patients treated with a 6-drug regimen did no better than those treated with a CHOP-like regimen. Some have interpreted these reports to mean that all patients with DLCL should receive CHOP, since they feel it to be "safer". I believe this is not a good interpretation of the available data for the following reasons:

1) When administered at maximum tolerated doses, CHOP has the same 5% treatment related mortality seen with all regimens.

2) When CHOP is given at reduced (i.e. "safer") doses it is not as effective.

3) It is not yet clear that all patients with DLCL are the same in their response to treatment. That is, some patients might have a higher chance for cure with one or another regimen.

My interpretation of the available data is that at the present time each oncologist should choose the regimen in which he/she has the most confidence and become expert in its use. By becoming an expert in the use of a particular regimen it is possible to minimize treatment related mortality and give patients the maximum chance for a good outcome. It is also important that clinical trials continue to identify the optimal treatment for each sub-group of patients with DLCL.

PHASE II TRIAL OF DICE (Dexamethasone, Ifosfamide, Cisplatin, and Etoposide) IN PATIENTS WITH NON-HODGKIN'S LYMPHOMA (NHL).

P. Goss, F. Shepherd, S. Buick, J. Scott, D. Hogg, S. Sutcliffe, E. Warner, D. Sutton, M. Baker. The Toronto Hospital, Toronto, M5G 2C4, Canada.

Eighteen patients (pts) with refractory NHL (11 primary nonresponders and 7 at relapse) were treated with DICE (dexamethasone 10 mg q6h, ifosfamide 1 g/m^2, cisplatin 25 mg/m^2, etoposide 100 mg/m^2, and mesna uroprotection) daily x 4 q28d. Thirteen male and 5 female pts, median age 65 yr (range, 21-74), have received a total of 45 cycles. Thirteen pts had stage IV, 1 stage III, and 4 stage II disease. Six pts had B symptoms and 8 had marrow involvement. Only 2 pts had had more than 1 previous chemotherapy regimen. The median time from last chemotherapy was 8 months (range, 1-23). It is too early to evaluate one pt, and 2 suffered early treatment-related deaths and have been classified as nonresponders. Six of 17 pts (35%) achieved CR (6-60+ wk) and 7 (41%) PR (4-29 wk) for an overall response rate of 76%. The median survival has not been reached, but 10 pts are alive 4-64 wk from the start of treatment. Five pts had nadir granulocyte counts less than 0.50 x 10^9/L; 5 required blood transfusions. Two pt deaths were related to sepsis. The platelet nadir was less than 50 x 10^9/L in 6 pts. Four pts had microscopic hematuria. Only 1 pt had grade III GI toxicity, and one had a transient episode of delirium and visual blurring. In summary, DICE is very well tolerated. Myelosuppression is the dose-limiting toxicity, particularly in pts with marrow involvement.

THE STANFORD EXPERIENCE WITH HIGH-DOSE ETOPOSIDE (VP-16) CYTOREDUCTIVE REGIMENS AND AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) IN HODGKIN'S DISEASE (HD) AND NON-HODGKIN'S LYMPHOMA (NHL). S.J. Horning, N.J. Chao, R.S. Negrin, R.T. Hoppe, G.D. Long, P. O'Connor, K.G. Blume, Stanford University Medical Center, Stanford, California

From December 1987 through March 1990, 77 patients (pts), 37 with HD and 40 with NHL, received 60 mg/kg etoposide (VP-16) in combination with 100 mg/kg cyclophosphamide (CY) and either 1,200 cGy fractionated total body irradiation (FTBI) or, for those previously treated with thoracic irradiation, 450 to 550 mg/m^2 carmustine (BCNU) prior to ABMT. Marrow from NHL pts was purged in vitro with a panel of monoclonal B and T cell antibodies and complement. Twenty-eight pts received FTBI/VP-16/CY and 49 received BCNU/VP-16/CY. All six toxic deaths occurred in pts treated with BCNU; fatal toxicities included veno-occlusive disease (2 pts), pneumonitis (1 pt), fungal infection (1 pt), and delayed cytopenia (2 pts). With a median follow-up of 1 year (range, 2 to 27 mo), 57 pts are alive and free from progressive disease. The actuarial survival and freedom from progression at 1 year are similar for the 28 pts receiving FTBI/VP-16/CY (85%, 74%) and the 49 pts receiving BCNU/VP-16/CY (79%, 72%).

Forty-five pts participated in prospective trials for which eligibility criteria were as follows: (1) less than 25% curability with conventional therapy (CT); (2) achievement of minimal disease state with CT; and (3) transplantation early in the course of disease. One year actuarial survival for 21 protocol participants with diffuse mixed or large cell NHL who were primary induction failures or developed recurrent disease after primary chemotherapy is 73%. One year actuarial survival for 18 pts with HD who were induction failures or developed recurrent disease after one or two primary chemotherapy regimens is 83%. While preliminary, both of these results are superior to those obtained with historical control subjects at a similar time period. One pt with Burkitt's NHL has been transplanted on a protocol for high-risk intermediate and high grade NHL in first remission. Five pts with follicular mixed or small cleaved NHL have also been transplanted in first remission.

Overall, these data demonstrate an acceptable rate of fatal toxicity (8%) among 77 pts treated with high-dose VP-16 regimens. The preliminary results are encouraging, but larger patient cohorts and longer follow-up periods are needed to address the curative potential of these regimens according to histology and clinical parameters of potential prognostic significance. With the early use of ABMT, especially among patients with low-grade lymphoma and HD, quality of life issues and the ability to deliver palliative therapy upon posttransplant relapse will also need to be addressed.

FACTORS AFFECTING THE OUTCOME OF AUTOLOGOUS BONE MARROW TRANSPLANTATION.

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Various protocols have been used at MSKCC to improve the results of autologous bone marrow transplantation (AuBMT) for hematopoietic malignancies. Our results suggest that the patients who undergo AuBMT in complete remission (CR) (after induction or reinduction treatment) do better than patients who undergo AuBMT in incomplete response (IR). After AuBMT, relapse and/or toxic complications are the main factors to improve upon in the future (Table). Pulmonary toxicity occurs mainly in patients with mediastinal disease. Factors that can decrease the relapse rate and toxicity will be discussed. The outcome of similar trials at other institutions will also be discussed. This study was supported by Morgan Murray Fund, National Leukemia Association and the United Leukemia Fund, and the Einard and Sue Sundin Fund.

Diagnosis/No.	% CR AuBMT	Preconditioning Regimen	Status After AuBMT: % Relapse CR	% Relapse IR	% Toxic Death CR	% Toxic Death IR	% Survival All Pts Median (mo)
Upfront NHL/14 Poor prognosis	43	TBI,CTX	20	20	0	0	79 (81)
Salvage NHL/15	33	TBI,CTX	80	50	20	30	13 (78)
Salvage NHL/26	23	TBI, etoposide, CTX	0	12	0	48	54 (40)
Salvage HD/22 Previous RT	32	BCNU, etoposide 250 mg/m^2 x 3, CTX, stopped	14	73	14	0	68 (20)
Salvage HD/13 Previous RT	31	BCNU,etoposide 350 mg/m^2,CTX	0	22	0	11	85 (5)
Salvage HD/24 No previous RT	25	TNI, etoposide, CTX	17	22	0	28	71 (24)

TBI = total body irradiation; CTX = cyclophosphamide; BCNU = carmustine; TNI = total nodal irradiation

THE PARMA INTERNATIONAL RANDOMIZED PROSPECTIVE STUDY IN RELAPSED NON-HODGKIN'S LYMPHOMA: FIRST INTERIM ANALYSIS OF 128 PATIENTS.

T. Philip, D. Bron, C. Guglielmi, A. Hagenbeek, B. Coiffier, C. Gisselbrecht, J.C. Kluin Nelemans, R. Somers, J.L. Misset, J. Van Der Lely, S. Jagannath, G. Rosti, J. Armitage, F. Chauvin. Centre Leon Berard - 28, rue Laennec 69008 Lyon, France, for the 43 international institutions.

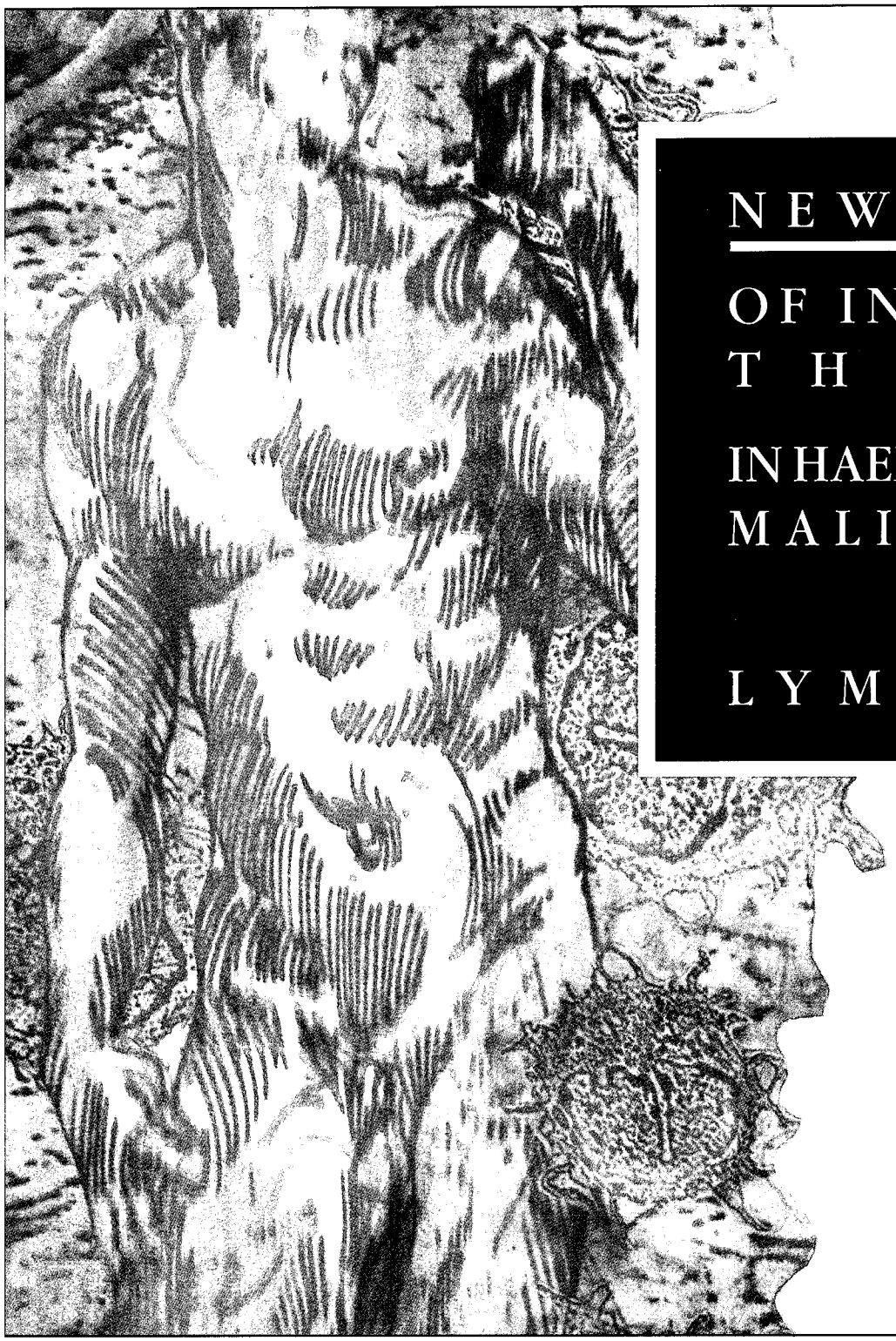
In order to compare conventional therapy with massive chemotherapy + autologous bone marrow transplantation (ABMT) in relapsed non-Hodgkin's lymphoma (NHL), a randomized multicenter study was initiated by the PARMA group. Since July 1987, 128 consecutive patients from 43 worldwide institutions were included in the study. All patients had intermediate- or high-grade NHL with previous complete remission (CR) and were included at time of first or second relapse. Age was less than 60 years. CNS and bone marrow relapses were excluded. Histologic proof of relapse was mandatory. After a complete staging, all patients received the same rescue protocol, ie, DHAP (dexamethasone, cisplatin, and cytarabine) for 2 consecutive courses at 3- to 4-week intervals.

A total of 128 patients are evaluable for response; 69 patients achieved partial response or CR after 2 courses of DHAP (54%). Patients relapsing on therapy (20%) have a lower response rate than patients relapsing off therapy (80%) (9% $\underline{v}$ 57%; $\underline{P} < .001$). Among these 69 patients, 62 were randomly assigned between 4 additional courses of DHAP (n = 34) or massive therapy with BEAC (carmustine, etoposide, cytarabine, cyclophosphamide) and ABMT (n=28). Radiotherapy of involved fields was performed after 6 courses of DHAP in the first arm, and before massive therapy and ABMT in the second one. Reasons for no randomization were progression (46.8%), patient refusal (2.3%), technical problems (1 patient), abnormal bone marrow cellularity (1 patient), hepatic dysfunction (1 patient), renal failure (1 patient).

The main end point is the failure rate at 2 years, ie, relapse or death from any cause.

There is no statistical difference in terms of toxic death rate. Comments and further results of the first interim analysis of this ongoing international study will be given in detail in this presentation.

Roche **cordially invites you to the Satellite Symposium**



NEW ASPECTS OF INTERFERON THERAPY IN HAEMATOLOGICAL MALIGNANCIES AND LYMPHOMAS

Chairman:
Professor A. H. Goldstone
(United Kingdom)

Wednesday, June 6, 1990
12.30 – 15.30 pm
Palazzo dei Congressi
Room B
Lugano

Preliminary Programme

Dr. R. Kurzrock (USA)	Molecular mechanisms of chronic myeloid leukaemia (CML) Overview of MD Anderson studies of interferon alpha in CML
Dr. M. Baccarani (Italy)	Italian multicenter study on ‹Roferon›-A in chronic myeloid leukaemia (CML) ‹Roferon›-A versus traditional chemotherapy in CML
Prof. H. Mellstedt (Sweden)	Interferon alpha combination therapy in multiple myeloma
Dr. A. Hagenbeck (The Netherlands)	Interferon alfa-2a maintenance in non-Hodgkin's lymphoma
Prof. G. Papa (Italy)	Interferon alfa-2a in cutaneous T-cell lymphoma
Dr. F. Giles (United Kingdom)	Interferon alpha in the treatment of chronic lymphocytic leukaemia