Abstracts of Satellite Symposia

The evolving role of anthracyclines in the treatment of malignant lymphomas

THE EMERGING ROLE OF IMMUNOTHERAPY IN NON-HODGKIN'S LYMPHOMA. J. P. Dutcher, Montefiore Medical Center/Albert Einstein Cancer Center, Bronx, NY, USA.

Clinical investigation of interferons (IFNs) has been ongoing for over 20 years, with major antitumor activity demonstrated against hematologic malignancies and some solid tumors. IFN has direct effects on cell proliferation mediated through its receptor. IFNs have also been shown to induce transcription of nearly 30 proteins, which have a multitude of actions within the cell, not all understood, and IFNs induce production of other cytokines which modulate the immune response and cell growth. Anti-proliferative effects in hematologic malignancies is at least a part of the mechanism of the clinical benefit observed. Clinical activity against lymphoid malignancies was demonstrated initially in the treatment of hairy cell leukemia which yielded complete and durable responses. Recently, IFN has demonstrated major activity in HTLV-I associated T-cell leukemia in combination with zidovudine and in cutaneous T-cell lymphoma, both alone and in combination with cisretinoic acid or PUVA. Clinical trials have explored the role of IFNs and interleukin-2 (IL2) in the more common B-cell malignancies, both as treatment of advanced disease and as potential maintenance therapy against minimal residual disease. More recently, studies have integrated IFN directly into lymphoma chemotherapy regimens with rather dramatic results, including enhanced response rates, as well as significantly improved disease-free survival and in some studies, in overall survival. Additional studies of both IFN and IL2 to upregulate the cellular immune response following autologous bone marrow transplantation in both leukemia and lymphoma are ongoing and early reports are promising.

GELF STUDIES OF INTRON A IN FOLLICULAR LYMPHOMAS. An Update on the Clinical Data Ph. Solal-Celigny for the GELF group (France & Belgium)

Some ten years ago, the GELF group initiated two clinical trials in patients with follicular lymphomas (FL). Patients were separated in 2 groups according to their tumor burden. Patients with any of the following criteria were considered to have a high tumor burden: any nodal or extranodal tumor mass with a diameter of more than 7 cm; involvement of at least three nodal sites, each of which had a diameter of more than 3 cm; systemic symptoms; substantial splenic enlargement; serious effusion, orbital or epidural involvement, or ureteral compression; and leukemia. Patients with low tumor burden were randomized between 3 treatment arms: • Watchful waiting until progression, followed by polychemotherapy; • Prednimustine 200 mg/m2 day x 5 days per month PO during 18 months; • INTRON A 5 MU/day subcutaneously during 3 months followed by 5 MU tiw during 15 months.
The goals of this trial were: • To prospectively follow the time to progression in untreated patients and thus to confirm the retrospective analysis of the Stanford group; • To confirm the efficacy of INTRON A in untreated patients and to compare its activity with that of a standard single-drug treatment.
Since October 1986, 182 pts have been considered to have a low tumor burden FL. 64 pts had no treatment, 59 pts were treated with prednimustine, 59 pts were treated with INTRON A. Clinical characteristics were similar in the 3 groups. The median follow-up is 48 months. The overall response rate was 56% in the prednimustine arm and 48% in the interferon arm. The median event-free survival was 20 months in the no treatment arm, 32 months in the prednimustine arm and 29 months in the INTRON A arm (N.S.). The overall survival was not different between the 3 groups.
Patients with a high tumor burden received the CHVP chemotherapy regimen (cyclophosphamide 600 mg/m2 D1, teniposide 60 mg/m2 D1, doxorubicin 25 mg/m2 D1, prednisone 40 mg/m2/day D1-D5). One cycle every 4 weeks during 6 months and then 1 cycle every 8 weeks during 12 months were administered. Chemotherapy was randomly given alone (CHVP arm) or with INTRON A 5 MU tiw subcutaneously during 18 months (CHVP + IFNα arm). The goals of this trial were to test the potential synergistic or additive effects of IFNα and cytotoxic agents known to be active in FL. The results of the first analysis of this trial have been detailed in a previous report (N. Engl. J. Med. 1993, 329: 1608). Briefly: • the overall response rate was greater in the CHVP + IFNα arm compared to CHVP alone (69% vs. 85%, p = 0.006); • although WHO grade >3 granulocytopenia was more frequent in the CHVP + IFN α arm, infectious complications were rare and moderate.
In the CHVP + INTRON A arm, 71% of patients could be treated as scheduled in the protocol. With a median follow-up of surviving patients of 48 months, survival data can now be updated. The median event-free survival was 34 months in the CHVP + IFNα arm compared to 18.5 months in the CHVP ARM ($P = 5 X10^{-4}$). The median actuarial survival is 61 months in the CHVP arm and 83 months in the CHVP + IFNα arm (p=0.009). The results of this final analysis confirm those of the first interim analysis.
The conclusion of the GELF trials may be as follows: • In patients with a low tumor burden, an initial no treatment policy does not have a negative influence on survival. As a single drug, interferon alpha has the same efficacy as an alkylating agent but a longer follow-up for definitive conclusions is needed; • In patients with a high tumor burden, a longer follow-up of the trial previously reported confirms that the addition of interferon alpha to a CHOP-like regimen significantly improves event-free and overall survivals. Toxicity of this combination was moderate and easily manageable.

QUALITY OF LIFE IN LOW GRADE LYMPHOMA: A Q-TWIST ANALYSIS OF THE GELF TRIAL. Bernard F. Cole, Philippe Solal-Céligny, Richard D. Gelber, Eric LePage, David Sugano, Aron Goldhirsch. Brown University, Providence, RI, Groupe d'Etude des Lymphomes de l'Adulte, Paris, France, Dana-Farber Cancer Institute, Boston, MA, Schering-Plough, Kenilworth, NJ and Ospedale Civico, Lugano, Switzerland

Recombinant interferon alfa when combined with cyclophosphamide, doxorubicin, teniposide and prednisone (CHVP) is effective for the treatment of non-Hodgkin's lymphomas. The Groupe d'Etude des Lymphomes de l'Adulte randomized, controlled clinical trial compared CHVP alone versus CHVP plus interferon alfa (CHVP+IFN) in 242 patients (New Engl J Med 329:1608-1614,1993). At 35 months median follow-up, the trial showed improvement in event-free survival ($P < 0.001$) and overall survival ($P = 0.2$) for CHVP+IFN. Despite these gains, the toxicity of interferon is a concern for patients and physicians. To address this, we evaluated the clinical trial using a method called Quality-adjusted Time Without Symptoms and Toxicity (Q-TWiST). Q-TWiST estimates the average time spent in a series of clinical health states differing in quality of life. Each state is weighted according to its quality of life on a utility scale from 0 = "as bad as death" to 1 = "as good as best possible health." The weighted durations are used to compare the treatments in terms of quality-of-life-adjusted survival. Three health states were identified: time with grade 3 or worse toxicity (Tox), time without disease progression and toxicity (TWiST), time following progression (Prog). The quality-adjusted survival endpoint was computed as: $u_{Tox} \times Tox + TWiST + u_{Prog} \times Prog$, where u_{Tox} and u_{Prog} are the utility weights; and Tox, TWiST and Prog denote the health state durations. Because direct patient data were not available for the utility weights, we compared the treatments across all combinations of utility values. Our analysis used a recent update of the clinical trial data with a median follow-up of 60 months. The median progression-free survival was 18.6 months for the CHVP group and 34.1 months for the CHVP+IFN group ($P < 0.001$). The median overall survival was 61.1 months for the CHVP group and 83.1 months for the CHVP+IFN group ($P = 0.009$). The table below shows the average health state durations in months according to treatment group. Our analysis indicated that CHVP+IFN provided more quality-adjusted time than CHVP alone for every possible pair of utility values. This benefit was significant ($P < 0.05$) in all cases where a higher value is placed on time with toxicity as compared to time with progression (i.e., $u_{Tox} > u_{Prog}$). The results of our analysis confirm the previously reported superior disease control with CHVP+IFN, and the Q-TWiST analysis demonstrates that interferon can be beneficial for the patient, even after accounting for the diminished quality of life associated with treatment toxicity.

Treatment	Tox	TWiST	Prog
CHVP	0.2	26.0	20.6
CHVP+IFN	2.6	33.9	15.5

SIGNIFICANT PROLONGATION OF DISEASE FREE SURVIVAL IN ADVANCED LOW GRADE NON HODGKIN'S LYMPHOMAS (nhl) BY INTERFERON ALPHA MAINTENANCE.
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In spite of a clear antilymphoma effect of interferon alpha (IFN-α) in low grade NHL its role and most appropriate place within the therapeutic strategy for advanced stage disease are still a matter of controversial debates. In several studies a prolongation of disease free survival (DFS) could be demonstrated by adding IFN-α to anthracycline containing initial cytoreductive regimens as well as by its application for maintenance treatment. In these settings the beneficial effect of IFN-α appears to be limited to the time of administration, however, and an increased relapse rate is usually noted within six to twelve months after the end of IFN therapy resulting in the merge of disease free and overall survival curves. In 1988, the German Low Grade Lymphoma Study Group started a prospective randomized comparison of IFN-α maintenance versus observation only in patients with advanced stage III and IV follicle center lymphoma (FCL=centroblastic centrocytic NHL according to the Kiel classification) and mantle cell lymphoma (MCL=centrocytic NHL) responding to an initial cytoreductive therapy with a combination of Cyclophosphamide, Vincristine, Prednisone (COP) or Prednimustine, Mitoxantrone (PmM). In contrast to the other studies IFN-α was given without a fixed time limitation until relapse or untolerable toxicity at a dose of 5 Mill. U/d 3 x weekly with dose adjustment to side effects. Until June 1995, 91 patients with MCL and 412 patients with FCL entered the study. The trial was monitored by a sequential test with working significance level 0.05. As of May 31, 1995, randomisation was terminated with 142 patients evaluable for DFS and toxicity because of a significant advantage in favor of IFN-α (Logrank-Test: p=0.0048). In the IFN-α group the estimated median DFS was 31 months as compared to estimated 12 months in the control. The projected DFS at 3 years accounted to 46% versus 22%, respectively. Side effects consisted predominantly of fever, myalgia and fatigue and required dose reduction in 70% of patients within the first 6 months while complete abrogation of treatment was experienced in 22% of cases, respectively. Although the effect on overall survival cannot be assessed at the present time, these data clearly demonstrate a prolonged effect of IFN-α maintenance in low grade lymphoma which provides a significant prolongation of DFS and the interval without the requirement of further cytostatic therapy in patients with advanced low grade NHL.

THE ROLE OF IMMUNOTHERAPY IN THE POST BONE MARROW TRANSPLANT SETTING FOR LYMPHOMA PATIENTS. B. Coiffier. Hospices Civils de Lyon, 69310 Pierre-Bénite, France.

High-dose therapy with hematopoietic stem cell rescue (bone marrow cell transplant or BMT) has been shown to be the best treatment for relapsing or PR patients after first line therapy. BMT may also be the best treatment for some subgroups of patients in first CR but with adverse initial prognostic parameters. However, only 30% to 40% of relapsing patients who respond to salvage therapy will have long-term disease-free survival. The remaining patients either do not respond to the salvage regimen or relapse after BMT. Possible causes of relapse after BMT are failure of high-dose therapy to eradicate lymphoma cells, reinfusion of lymphoma cells, and failure of the immune system to eradicate the last lymphoma cells. Negative purging or positive selection of CD34+ cells may be used to decrease graft contamination. Phase II trials of different conditioning regimens have to be tested to improve the post-BMT CR. Stimulation of immune reactions or immunotherapy may improve the immunodeficiency induced by the procedure and help the immune destruction of lymphoma cells.

Immune modulation with interleukin-2 (IL-2) or interferon has induced clinical responses in patients with advanced disease and has prolonged disease-free survival in prospective randomized trials. It has been proven that transplanted patients had a poor response to different stimuli and that this response may be improved with IL-2 administration. If this immune deficiency is certain, its exact mechanism and its role in relapse post-BMT are not known. A graft-versus-lymphoma effect has been demonstrated in allogenic BMT and witness of the benefit of immune system stimulation. If immunotherapy has any value it will be in the state of minimal residual disease as it is observed after BMT. Preliminary results showed a possible benefit of interferon or IL-2. Several prospective trials randomizing interferon or IL-2 versus observation are currently activated.

THE USE OF ORAL IDARUBICIN, CHLORAMBUCIL AND DEXAMETHASONE IN LOW GRADE NON-HODGKIN'S LYMPHOMA S J Proctor, P R A Taylor, Department of Haematology, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP

Low grade non-Hodgkin's lymphomas (NHL) are commonly treated by single alkylating agents such as chlorambucil. The advent of the new cytotoxic anthracycline idarubicin has prompted an assessment of its efficacy within current treatment regimens in the management of patients with low grade NHL. The identification of discrete prognostic[1] groups of patients (classified as best, intermediate and worst risk) with low grade NHL has allowed an assessment of the efficacy of treatment with respect to the prognostic risk status of patients. Preliminary analysis of a phase II study has shown that idarubicin 10 mg/sqm daily for 3 days plus chlorambucil 20 mg/sqm daily for 3 days plus dexamethasone 4 mg bd for 5 days given for 6 courses shows an overall response rate of 77%. The median age of the population treated was 54 years with 24 females and 38 male patients. 79% were Stage IV disease, 76% of patients had follicular histology and the remainder other low grade histological groups. By risk index 63% of patients were intermediate risk, 11% poor risk and 26% good risk. Haematological toxicity was minimal and no alopecia was seen. The overall response rate was 77%. The combined groups of patients achieving CR plus CR(M) plus CR(U) was 50% with patients achieving GPR and PR 27%. 23% of patients showed responses less than PR. Overall the response rate for those with follicular histology was 88%. The overall survival is good at 40 months at 85%, but the overall median event-free survival is 20 months. The conclusion of the phase II study to date indicates that short course all oral idarubicin, chlorambucil and dexamethasone is a very tolerable regimen with minimal toxicity providing equivalent responses to that seen using other combinations including intravenous anthracyclines. Currently a randomised trial is assessing the combination against chlorambucil and dexamethasone alone and further information is being obtained about responses in the risk groups.

CR = complete response, CR(M) = complete response with some residual marrow involvement, CR(U) = complete response, no marrow repeated, GPR = good partial response, PR = at least 50% improvement

1. Leonard, R.C.F., Hayward, R.L., Prescott, R.J., Wang, J.-X., Allan, N.C., Barrett, A., Das, S.N., Dawson, A.A., Heppleston, A., Lessells, A.M., Lucie, N.P., Lucraft, H.H., Mackie, M.J., MacLaren, K.S., Parker, A.C., Proctor, S.J., Sarkar, T.K., Sheehan, T., Soukop, M., Steward, W.P., and White, J.M. The identification of discrete prognostic groups in low grade non-Hodgkin's lymphoma. *Ann Oncol* 2:655-662, 1991.