Abstracts of Satellite Symposia

The evolving role of antichymotrypsin 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 are 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-1 associated T-cell leukemia in combination with zidovudine and in cutaneous T-cell lymphoma, both alone and in combination with cisretinoid 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.


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 possible healthy.” 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: TQTox + TQTWIST + TWIST + Prog, where Tox, TWIST, and 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., Tox > 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.

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

Some years ago, the GELY 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 more than 3 lymph node sites; splenic enlargement; extralymphatic effusions, orbital or epidural involvement, or severe compression; and leukemia. Patients with low tumor burden were randomized between 2 treatment arms: "Watchful waiting" until progression, followed by polychemotherapy; + Prednisolone 200 mg/day x 5 days per month PO during 18 months; + INTRON A 5 MU/day subcutaneously during 3 months followed by 5 MU once every 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 January 1996, 182 pts have been considered to have a low tumor burden FL. 64 pts had no treatment, 39 pts were treated with prednisolone, 39 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 26% in the prednisone arm and 48% in the interferon arm. The median event-free survival was 20 months in the no treatment arm, 32 months in the prednisolone arm and 29 months in the INTRON A arm (NS). The median overall survival for all groups was 43 months. Patients with a high tumor burden received the CHVP chemotherapy regimen (cyclophosphamide 600 mg/m2 i.v., doxorubicin 60 mg/m2, dexamethasone 21 mg/m2, Vincristine 1 mg/m2 x 3 every 3 weeks). The dose was decreased for the 5th, 6th and 7th cycles. The overall response rate was 80% (49/62) with the CHVP arm or with INTRON A 5 MU subcutaneously during 18 months (CHVP + IFN arms). The goals of this trial were to test the potential synergistic or additive effects of IFN’s and cytostatic 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 + IFN arms compared to CHVP alone (65% vs. 49%; P = 0.006), both in relapse and in refractory disease. The median event-free survival was 34 months in the CHVP + IFN arm compared to 18.3 months in the CHVP arm (P = 0.015). The median overall survival was 61 months in the CHVP arm and 83 months in the CHVP + IFN arm (P = 0.009). The results of this final analysis confirm those of the first interim analysis. The conclusion of the GELY trials may be as follows: in patients with a low tumor burden, a chronic interferon 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 confirmed the addition of interferon alpha to a CHVP-like regimen significantly improves the event-free and overall survival. Toxicity of this combination was moderate and easily manageable.


In spite of a clear antitumor effect of interferon alpha (IFN-a) in low grade NHL, its role and most appropriate place within the therapeutic strategy for advanced stage disease are still a matter of considerable debate. Concerns have been raised with regard to development of drug resistance (DPR) which could be demonstrated by adding IFN-a to anthracycline containing initial cytoreductive regimes as well as by its application for maintenance treatment. In these settings the beneficial effect of IFN-a appears to be limited in 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-a maintenance versus observation only in patients with advanced stage III and IV follicle center lymphomas (FCL) with the same clinical characteristics. Twelve centers participating in this study were randomized with regard to the treatment of IFN-a. Maintenance was performed with IFN-a 3 million units/m2 i.m. three times a week for 12 months. In the control group, observation was planned. At the end of the maintenance phase, patients are assigned to a chemotherapy or observation arm. In the chemotherapy arm, chemotherapy was performed with a combination of Cyclophosphamide, Vincristine, Prednisone (COP) or Prednimustine, Miloxantrone (PMX). In contrast to the other studies IFN-a was given without a fixed time limitation until relapse or unacceptable toxicity at a dose of 5 Ml. U/m2 3 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 significant level 0.05. As of May 31, 1995, randomization was terminated with 142 patients evaluable for DFS and toxicity because of a significant advantage in favor of IFN-a (Logrank-Test: p=0.048). In the IFN-a group the estimated median DFS was 51 months as compared to estimated 12 months in the control. The projected DFS was 92% after 5 years and 73% after 7 years. 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 expressed in 22% of cases, respectively. Although the effects on DFS cannot be assessed at the present time, these data clearly demonstrate a pronounced effect of IFN-a maintenance in low grade lymphomas 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, reinfection 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 allogeneic 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.H.A. Taylor, Department of Haematology, Royal Victorian 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 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/m² daily for 3 days plus chlorambucil 20 mg/m² 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. 78% were Stage IV disease, 76% of patients had follicular histology and the remainder other low grade histological groups. By risk index 83% of patients were intermediate risk, 11% poor risk and 6% 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