Highlights from the 40th Annual Meeting of the American Society of Clinical Oncology
New Orleans, Louisiana, June 5-8, 2004

Non-Hodgkin's Lymphoma NEWS

Current perspectives on treatments for NHL: CHOP, rituximab, hyper-CVAD, and CVP

By Frieda Pierce, PhD

NEW ORLEANS—The oral session at ASCO on Lymphoma Including Transplantation encompassed various perspectives on a number of different treatment regimens and combination therapies for NHL. **David C. Dale, MD**, from the University of Washington, Seattle, presented a nationwide survey of suboptimal chemotherapy delivery in patients with aggressive NHL conducted by the Awareness of Neutropenia in Chemotherapy (ANC) Study Group. There were 6314 patients who were treated with chemotherapy between 1993 and 2001 at 567 oncology practices in the US. The ANC Study Group noted the demographics and clinical characteristics of the patients and the cycle-specific information, including actual chemotherapy doses and intervals with pretreatment blood cell counts. Dr Dale said that the retrospective analysis of the records of >4500 patients with aggressive NHL treated with CHOP or CHOP-like chemotherapy in the community setting showed that there were substantial reductions in chemotherapy dose intensity in nearly half the patients. He added that this dose reduction can negatively affect the cure rate and survival of these patients. The ANC Study Group found a number of factors to be associated with reduced dosing: old age, poor performance status, advanced stage disease, earlier year of first treatment, and practice site. Dr Dale explained that this study, whose primary goal was to determine the average reduced-dose intensity regimens in NHL patients, indicates that supportive care in patients who receive reduced dosing regimens should be evaluated in prospective trials.

In the same session, a randomized intergroup trial of first-line treatment comparing CHOP with or without rituximab for patients ≤60 years with diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) was presented by **Michael Pfreundschuh, MD**, from the Saarland University Medical School, Homburg, Germany. The 824 patients recruited to this trial from May 2000 to October 2003 had an International Prognostic Index score of 0 or 1; some patients had stage I bulky disease and 25% had stage III/IV disease. The endpoint was defined as time to treatment failure, which

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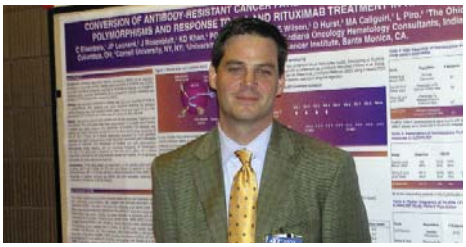
IL-2 augments rituximab's efficacy in refractory/relapsed non-Hodgkin's lymphoma patients

NEW ORLEANS—A number of posters on improving rituximab sensitivity in non-Hodgkin's lymphoma (NHL) patients were presented at the annual meeting of ASCO. At the poster session on Developmental Therapeutics: Immunotherapy, **Charles Eisenbeis, MD**, from Ohio State University, Columbus, described data on the introduction of interleukin (IL-2; Proleukin®) to the treatment regimen with rituximab and showed improved outcome in refractory patients. Rituximab exerts its toxic effect through recognition and binding to CD20 on the tumor cell, which subsequently interacts with natural killer cells through the Fc portion of the antibody. In certain patients, Dr Eisenbeis said, this mechanism is inefficient due to polymorphisms in the Fcγ receptors. IL-2 expands and activates natural killer cells carrying the Fcγ receptors, enhancing the antibody efficacy.

Dr Eisenbeis and colleagues applied this principle to relapsed/refractory non-Hodgkin's lymphoma patients in a phase II trial. To date, 44 patients were enrolled in the trial. They were treated weeks 1-4 with IV rituximab at 375 mg/m²/week. IL-2 was administered subcutaneously 3 times per week at 14 MIU weeks 2-5 and at 10 MIU weeks 6-9. Of 27 evaluable patients, 4 showed a response (1 complete and 3 partial) and 4 patients had stable disease. Of the responders, their genotypes were evaluated and 4 had the 158F/F polymorphism. Dr. Eisenbeis and his group concluded that these data show that IL-2 may overcome the low affinity of rituximab for the FcγR and restore its effectiveness in these patients. ♦



Charles Eisenbeis, MD, poses in front of the poster he presented on IL-2 and rituximab.

Clinical responses to rituximab are dependent on FcγR polymorphism genotypes

NEW ORLEANS—**Steven P. Treon, MD, PhD**, from the Dana-Farber Cancer Institute, Boston, presented a poster at ASCO on polymorphisms in FcγRIIIA (CD16) receptor expression and their association with clinical response to rituximab in Waldenström's macroglobulinemia (WM). The potency of antibody-mediated cytotoxicity is dependent on the affinity of Fcγ receptor interactions between the antibody and natural killer cells. Polymorphisms in the Fc receptor can reduce the binding affinity and consequently reduce the effectiveness of rituximab therapy. Dr Treon explained that 58 WM patients treated with rituximab had their FcγRIIIA receptors examined by sequencing their DNA coding regions. These patients showed two distinct but linked polymorphisms (FcγIIIA -48 and -158). Patients with FcγR -48L/H or -L/R and with 158 V/F or V/V showed higher major responses, however, because these polymorphisms are linked between -48 and -158. Dr Treon said that these findings suggest that polymorphisms at FcγRIIIA-158 are the most important predictors of response to rituximab. Polymorphism testing may distinguish patients who benefit from rituximab alone versus combination with chemotherapy. "FcγIIIA CD16-158V/V and FcγIIA CD32-131H/H were favorable FcγR genotypes and are associated with better clinical outcomes," he said.

Attendees at the 40th annual meeting of ASCO view the exhibits.

In an oral presentation of Leukemia, Lymphoma, and Transplantation, **Wen-Kai Weng, MD, PhD**, from Stanford University,

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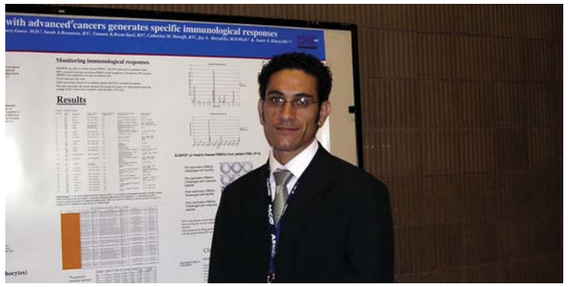
Interleukin-2 with mutant p53 vaccination generates immunologic responses in advanced cancers

NEW ORLEANS—In a study of 24 patients with advanced cancers and mutated p53, vaccination with specific mutant p53 produced immunologic responses, reported **Ramy A. Ibrahim, MD**, from the National Cancer Institute, Bethesda, Maryland. Tumor suppressor p53 is often mutated in many forms of human tumors, he said, during a poster discussion on Developmental Therapeutics: Immunotherapy at ASCO. These mutated genes produce proteins that are processed and displayed on HLA molecules as short peptides. Animal studies have shown that vaccination with mutated p53 peptide can generate cytotoxic T cells that target and kill tumor cells. Dr Ibrahim reported that autologous peripheral blood mononuclear cells (PBMC) from the patients were cultured with the p53 peptide and granulocyte macrophage stimulating factor for 48 hours. These were then administered to the patients intravenously. Subsequent administrations of PBMC were cultured with p53 peptide and interleukin-2 (IL-2). These cells were administered along with 6 MIU/m²/day of IL-2 on days 15-19 and days 22-26. The progression-free survival in 20 evaluable patients was twice as long as with conventional treatment, Dr Ibrahim said. Nine of the patients produced higher levels of interferon-gamma in their T cells. This was observed only with mutant p53 peptide and not with a control peptide. "Three patients are still alive after 40 months compared to conventional treatment," said Dr Ibrahim, "and overall survival is statistically significant." This novel technology provides promising treatment for immunologically deficient patients. ♦



Ramy A. Ibrahim, MD, presented results during a poster discussion at ASCO of a study on vaccination with mutant p53 in advanced cancers.

Cytokines enhance immunologic responses in follicular lymphoma

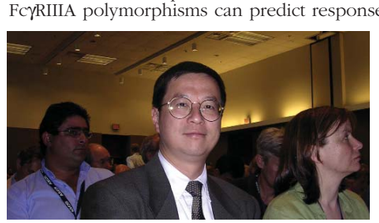
NEW ORLEANS—CD20 antibody positive CD8 cells were shown to kill tumors in follicular lymphoma, **Eric Chen, MD**, from the Fred Hutchinson Cancer Center, Seattle, Washington, reported in a poster discussion on Developmental Therapeutics: Immunotherapy at ASCO. Peripheral blood mononuclear cells were electroporated with an antiCD20 chimeric T-cell receptor plasmid and cultured using interleukin-2. The cells were grown in antibiotic-containing media to select for cells carrying the introduced plasmid. CD8 positive cells were selected using immunomagnetic bead technology and the clones were confirmed by flow cytometry. These cells were used in vitro and in vivo to examine natural killer cell activity. Dr Chen and his colleagues concluded that this method proves that CD20 positive cytotoxic T cells were effective in vitro and in vivo, and a phase I trial is planned in patients with relapsed follicular lymphoma. "The use of CD8 positive T cell selection prior to transfection with CD20 antibody provides a growth advantage to these T cells," Dr Chen said. "IL-15 was also tried in the culture medium and provided greater growth advantage over IL-2."

In another poster presentation, **Ian Davis, MD**, from the Ludwig Institute for Cancer Research, Melbourne, Australia, showed that interleukin-2 augments antibody cG250 activity in advanced renal cell carcinoma. ♦

Eric Chen, MD, after the poster discussion on immunotherapy at ASCO.

Clinical responses, *continued*

Stanford, California, also presented data on the clinical importance of FcγRIIIA polymorphisms, but in this investigation, their relationship to anti-idiotype vaccination was studied. A target of immunotherapy is the Ig idiotype (Id) expressed by B cell lymphoma. Ig idiotype vaccination can induce a humoral and/or cellular immune response with anti-Id antibodies. Since specific FcγRIIIA polymorphisms can predict response to rituximab, Dr Weng explained that this study examined the effect of FcγRIIIA polymorphisms and the immune response produced by Id vaccination on the clinical response in follicular lymphoma patients. Between 1998 and 2001, 155 patients received induction chemotherapy followed by Id vaccination. Tumor biopsies indicated that anti-Id antibody binds tumor cells. The 134 patients in first remission who received induction chemotherapy had follicular lymphoma grade I, II, or III. Longer freedom from progression (6.2 yrs) was seen in those patients who showed a humoral response, he said. Patients with FcγRIIIA-V/V genotype had a longer time to progression than those with V/F or F/F (see table). In contrast, neither cellular immune response nor polymorphisms in FcγRIIA-H/H, -H/R, and -R/R showed any impact on freedom from progression. "Fcγ receptors had no relationship with outcome following chemotherapy alone," Dr Weng said, "but favorable outcome using chemotherapy with anti-Id shows the importance of Fcγ receptors, which is probably due to its role in antibody-dependent cellular cytotoxicity." ♦



Wen-Kai Weng, MD, PhD, after an oral presentation on the FcγRIIIA polymorphisms.

FcγRIIIA polymorphisms and time to disease progression with Ig idiotype vaccination

FcγRIIIA polymorphisms	V/V	V/F	F/F
Time to progression (years)	8.2	2.7	2.9

Educational symposium features historical perspective on the treatment of NHL

By Frieda Pearce, PhD

NEW ORLEANS—At an ASCO Educational Symposium preceding the 40th annual meeting of the American Society of Clinical Oncology, **James Armitage, MD**, from the University of Nebraska Medical Center, Omaha, gave an overview of the treatment of non-Hodgkin's lymphoma (NHL) in a talk entitled, Aspects and New Horizons in Breast and Lung Cancers and Non-Hodgkin's Lymphoma. Although a hallmark of NHL is the Reed-Sternberg cell, there are many difficulties in classifying this disease, said Dr Armitage. The diagnostic accuracy in determining NHL, as reported by various cooperative groups, is 56% for SWOG, 56% for the Southeastern Cancer Study Group (SECSG), and not reported for ECOG.

With the availability of newer diagnostic techniques as well as in vitro information, a new lymphoma classification system is being developed, the World Health Organization Classification of Lymphoid Malignancies, which recognizes the distinct molecular, morphologic, and genetic characteristics of different lymphoma subtypes. Dr Armitage said he believes that more accurate diagnosis, together with important prognostic factors, will provide useful information for selecting and designing appropriate therapies for patients with aggressive NHL. He cited Rosenwald et al, who in the New England Journal of Medicine in 2002 said that molecular profiling by DNA microarray technology can predict survival in diffuse large B-cell lymphoma (DLBCL).

"For nearly 20 years, CHOP has been the gold standard of therapy for aggressive non-Hodgkin's lymphomas, curing about 30% of patients with diffuse large-cell NHL," said Dr Armitage. In the early 1970s, SWOG compared CHOP with other chemotherapy combinations in patients with advanced forms of mycosis fungoides. CHOP in stage I, II localized disease has a two times better outcome than in disseminated bulky stage II, III, or IV disease.

For minimal localized disease, Dr Armitage indicated that involved field radiotherapy (IFR) has had good results. He referred to a SWOG study, with follow-up for 8 years after randomization, which has shown that CHOP with radiotherapy is better than CHOP alone. A GELA study examined CHOP with or without IFR in patients over 60 years of age. That group concluded that patients 70 years and older fare better without radiotherapy (CHOP alone, overall survival 65%; CHOP with IFR, 49%).

James Armitage, MD, after his talk at an ASCO Educational Symposium

Dr Armitage also mentioned an LNH93-1 study in younger patients that examined doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP) against CHOP with IFR in patients stratified on the basis of bulk at randomization. This arm showed a better event-free survival rate than the CHOP with IFR arm when followed out to 9 years.

In an attempt to improve the treatment of disseminated DLBCL, Dr Armitage noted that several study groups have varied the chemotherapy regimens in terms of dose escalation, length of cycles, and the addition of suitable antibodies. The German Lymphoma Study group compared twice-weekly CHOP with thrice-weekly CHOP in aggressive lymphoma patients and found that overall survival was better in patients >60 years. Elderly patients are known to benefit from 14-day cycles of CHOP given with granulocyte colony-stimulating factor. In patients <60 years, the relapse rate was less with CHOEP (CHOP with etoposide) than with CHOP alone. He indicated that this study will be published in Blood this year.

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Effect of BCL-2 and BCL-6 on prognosis in non-Hodgkin's lymphoma patients

NEW ORLEANS—**Pierre Morel, MD**, from the Hôpital Schaffner, Lens, France, presented in an oral session an interim analysis for the GELA group on autologous stem cell transplantation (ASCT) as consolidation therapy for patients with low-intermediate risk diffuse large B-cell lymphoma (DLBCL) and BCL-2 overexpression. Dr Morel explained that this study examines whether ASCT overcomes the negative prognostic effect of BCL-2 overexpression, as reported in the New England Journal of Medicine in 2002. The ACVBP (adriamycin, cyclophosphamide, vindesine, bleomycin, prednisone) regimen with conventional consolidation therapy yields a 2-year event-free survival of 71% in DLBCL, he observed. Of the 272 patients aged 18-59 years stratified according to BCL-2 expression from 1999-2002, 151 showed BCL-2 overexpression and 121 did not. There was no difference in the toxicity of induction and complete response rates between the BCL-2 positive and negative population, he reported. This analysis shows that there is an advantage to up-front ASCT in DLBCL and indicates that ASCT may overcome the adverse prognostic factor of BCL-2 expression, Dr Morel added. It may be necessary to carry out molecular profiles of patients for BCL-2 expression prior to treatment. Newer therapies include BCL-2 antisense molecules, which represent targeted therapy in these patients.

Kenneth S. Wilson, MD, from the British Columbia Cancer Agency, Victoria, British Columbia, Canada, presented data at the poster discussion on Leukemia, Lymphoma and Transplantation that CHOP with rituximab (CHOP-R) treatment also overcomes poor prognosis of BCL-2 positive patients with DLBCL. Patients >60 years with DLBCL were treated with CHOP-R by the GELA group and superior survival was seen in these patients. Based on these studies, said Dr Wilson, the British Columbia Cancer group adopted CHOP-R as therapy in DLBCL patients. This study examined whether the patients whose tumors tested positive for BCL-2 still had poor prognosis. Eighty-nine patients were treated with CHOP-R from 2001 to 2003. Dr Wilson confirmed that the groups had similar International Prognostic Index distribution even though 62% of the patients had 50% of their tumors register the presence of BCL-2. Dr Wilson and colleagues concluded that this study showed that CHOP-R negated the adverse prognostic effect of the presence of BCL-2, and these patients showed similar survival as those DLBCL patients without BCL-2 expression in their tumors. Dr Wilson stated, "CHOP-R does better in the BCL-2 group in terms of overall survival."

Riccardo Dalla-Favera, MD, from the Columbia University Health Sciences Division, New York, examined the activity of BCL-6 in regulating p53-dependent apoptosis at the special session at ASCO entitled, International Symposium: Lymphoproliferative Diseases. Using a Ramos cell for the investigations, Dr Dalla-Favera and colleagues established that BCL-6 sits on the promoter of p53. BCL-6 also directly controls the expression of B7-1/CD80, a costimulatory receptor involved in B-T cell interactions critical for the development of T cell-mediated antibody responses. Upon initiation of CD40 signaling, transcription of the CD80 gene is induced by the nuclear factor (NF)-kappaB transcription factor. Dr Dalla-Favera's group showed that BCL-6 prevents CD40-induced expression of CD80 by binding its promoter region in vivo and suppressing the translocation of NF-kappaB to the nucleus. BCL-6 also can regulate p21-mediated growth arrest and p73-mediated apoptosis. "BCL-6 suppresses a p53 response to physiologic and genomic alterations," Dr Dalla-Favera said. In about 40% of DLBCL patients, there are mutations in the BCL-6 protooncogene, which results in changes to the CD40 signaling pathway.

Additionally, he said that chromosomal translocations also affect two adjacent BCL-6 binding sites located within the first noncoding exon of the gene and prevents BCL-6 from binding its own promoter, thereby disrupting its negative autoregulatory circuit. Further experiments using a mouse knock-in model with deregulation of BCL-6 expression results in proliferation of B cells. Monoclonality gives rise to a mouse with DLBCL, whereas polyclonality results in lymphoproliferative disorders. "BCL-6 will make a good therapeutic target. Time to treatment failure by BCL-6 induction has a favorable outcome," said Dr Dalla-Favera. ♦