Cytokine receptors on T cells such as the IL-2 receptor (IL-2R) are exceptionally valuable targets for immunotherapy since they are expressed by abnormal T cells of select lymphoid malignancies but not by normal resting cells. For example, human T-cell lymphotropic virus I (HTLV-I)-encoded tax induces the expression of IL-2 and the IL-2R on malignant adult T-cell leukemia (ATL) cells. To exploit the difference in receptor expression between normal and malignant T cells we have introduced different forms of IL-2R-directed therapy including an unmodified antibody to IL-2Rα (anti-Tac), humanized (Hu)-anti-Tac, as well as this antibody armed with *Pseudomonas exotoxin* or α- and β-emitting radionuclides (e.g., ⁹⁹mTc and ⁶⁷Cu). In particular, six of 19 patients with ATL treated with Mu-anti-Tac underwent a remission. Furthermore, the humanized version of anti-Tac (e.g., Daclizumab) was shown to prevent renal allograft rejection and has been approved by the FDA, USA for sale. In subsequent clinical trials involving ATL patients treated with anti-Tac armed with ⁹⁹mTc over 50 percent of the patients treated underwent a partial or complete remission. New agents under development include both antibodies and small molecules directed toward receptors and signaling elements shared by cytokines (e.g., IL-2, IL-4, IL-7, IL-9, IL-15) that stimulate T cells. Thus insights concerning receptors and signaling pathways used by leukemia/lymphoma cells taken in conjunction with the ability to produce Hu-antibodies armed with α- and β-emitting radionuclides are providing novel perspectives for the treatment of leukemia/lymphoma.
CURRENT STRATEGIES IN THE TREATMENT OF HODGKIN'S DISEASE

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The treatment strategies in Hodgkin's disease (HD) are changing strikingly. Based on numerous reports on the fatal long-term toxicities of radiation therapy, especially the high number of solid second cancers, extended field (EF) irradiation is abandoned now by most study groups. Thus, in early stage HD EF irradiation, which has been the standard therapy over decades, is substituted by combined modality treatment (CMT), i.e., few cycles of mild chemotherapy for control of occult disease followed by irradiation in the involved field (IF). In their actual clinical trials for early stage HD the German Hodgkin's lymphoma study group (GHSG) as well as the European Organization for Research and Treatment of Cancer (EORTC) raise the question for the intensity of chemotherapy (number of cycles) and radiotherapy (dose). Similarly, in intermediate stage HD, where CMT has already been the standard, quality and quantity of chemotherapy given before radiotherapy and radiation dose in the IF are analyzed in current European Consensus trials. These new strategies for the treatment of early and intermediate stage HD are expected to reduce long-term toxicity without minimizing the excellent treatment results. Quite another situation is found in advanced stage HD. So far, a disappointing long-term survival (SV) of about 60 % only could be achieved with standard therapy protocols. New dose-intensified protocols like the Stanford V protocol or the IDEXX regimen of the GHSG now for the first time have shown that freedom from treatment failure (FFTF) and possibly also SV can be improved significantly. The challenge for the future will be to keep the balance between improvement of treatment results by more aggressive induction therapy and the decrement of survival by therapy induced causes of death.

DIFFUSE LARGE CELL LYMPHOMA

Richard I. Fisher, M.D., Coleman Professor of Oncology, Cardinal Bernardin Cancer Center, Loyola University Medical Center, Maywood, IL, U.S.A.

Introduction: During the 1970’s and 1980’s single institution Phase II trials with so-called "second and third generation" chemotherapy regimens for advanced stage patients appeared to demonstrate nearly a doubling of the complete remission rate and overall survival compared to the “first generation” combination chemotherapy studies. Unfortunately, randomized trials comparing standard therapy, CHOP, to the “third generation chemotherapy regimens” all still show no difference in time to treatment failure, or overall survival, however the cost and toxicity of the new regimens was higher. Thus CHOP remains the best available standard of care; the recognition of this fact has resulted in significant cost savings and the avoidance of unnecessary toxicity. However, based on the fact that fewer than 50% of all patients are cured and, as noted subsequently, we can now identify subsets of patients with lower cure rates, it is absolutely essential that oncologists develop new and improved therapeutic approaches for patients with advanced stage, aggressive histology non-Hodgkin's lymphoma.

Treatment Strategies: Investigators are currently utilizing several different approaches to attempt to improve these treatment outcomes. These include: 1) the identification of new active drugs for the treatment of lymphoma, 2) the use of colony stimulating factors, CSFs, to allow dose escalation of the active but myelotoxic drugs. 3) the use of strategies which may overcome the problem of resistance to chemotherapy which is the ultimate cause of treatment failure in the majority of patients, and 4) the use of prognostic factors prior to therapy to identify patients who might be candidates for aggressive approaches including intensive therapy with either bone marrow or peripheral stem cell support. Available results of these trials will be reviewed. Following these preliminary leads, the Lymphoma Committees and the Bone Marrow Transplant Committee of SWOG, ECOG, and CALGB have agreed to jointly conduct a randomized clinical trial of early versus delayed high dose therapy for patients with high-intermediate and high risk large cell non-Hodgkin’s lymphoma. Patients under the age of 65 years will each receive 5 cycles of CHOP; responding patients will then be randomized to receive either 3 more cycles of CHOP or 1 additional cycle of CHOP followed by high dose therapy with autologous stem cell rescue. Patients on the standard CHOP treatment who relapse will then receive the same high dose therapy. If this study confirms the benefit of high dose therapy for this patient group, subsequent trials will attempt to increase the number of responding patients who become eligible for high dose therapy.

FOLLICULAR LYMPHOMA: HAVE WE MADE ANY PROGRESS?

Sandra J. Horning, MD. Stanford University, Stanford, CA

The t(14;18), the hallmark of follicular lymphoma, appears to be necessary but not sufficient for tumor development. Data suggest that in addition to conventional management options such as watchful waiting and alkylating-based chemotherapy, new agents have been introduced and data with therapeutic alternatives have matured. The conflicting interferon results have been subjected to meta-analysis and additional results have been reported from two large clinical trials. Fludarabine has been compared with CVP as primary treatment in a randomized trial. Combination therapy with alkylators or mitoxantrone and fludarabine has been more broadly tested. A major development is therapy targeted to the CD20 antigen, expressed on nearly all follicular lymphomas. The unconjugated chimeric anti-CD20 (rituximab) received approved for recurrent disease based on response rates of about 50%. Higher response rates have been reported in a number of studies with 111 or 131 conjugated to anti-CD20. Meanwhile, the data with high dose chemo-radiotherapy and autotransplantation have matured. Despite longer remission durations, the absence of a definitive survival benefit and late effects lessen enthusiasm for this approach. Several investigators continue with individualized approaches to harness the immune system for vaccine or cell-based therapies. In recognition of the heterogeneity of follicular lymphoma and the inadequacy of the International Index, an international effort is underway to assay prognostic factors. With a plethora of effective but non-curative treatments, the current challenge is sequencing of therapy for optimal palliation of individual patients and design of novel combination programs for clinical trials with curative intent.

WORKSHOP ON BIOLOGICAL PROGNOSTIC FACTORS IN AGGRESSIVE NON-HODGKIN'S LYMPHOMAS.

Gilles Salles, Centre Hospitalier Lyon-Sud, France; Margaret A. Shipp, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

The heterogeneity in outcomes in aggressive non-Hodgkin's lymphomas prompts the development of clinical prognostic factors which identify patients with different likelihoods of being cured of their disease. However, these clinical prognostic factor models are based on clinical features that are, in large part, surrogate variables for the biological heterogeneity of these diseases. The workshop on biological prognostic factors in aggressive non-Hodgkin's lymphomas will be held to review recent developments in this area and to organize follow-up collaborative studies. At the workshop, the definitions of the aggressive non-Hodgkin’s lymphomas will be discussed and the specific cytogenetic abnormalities implicated in these diseases will be reviewed. Abnormalities of lymphoid development, signaling and apoptotic pathways will be discussed, including the role of bcl-6 in germinal center development and the normal lymphoid counterpart for diffuse large B-cell lymphomas (DLBCL). Additional areas of specific emphasis will include the role of NPM1/ALK in anaplastic large cell lymphomas, specific abnormalities of bcl-2 family members in DLBCL, and recent data regarding tumor suppressor genes in these diseases. In addition, the relationship between tumor cells and their microenvironment will be reviewed with particular emphasis on tumor cell immunogenicity, host immune response, lymphocyte migration and trafficking and lymphocyte cytokine production. In a final session, newly developed methods for the analysis of biologic prognostic factors, such as comparative genomic hybridization and microarray analysis, will be summarized.
MANTLE CELL LYMPHOMAS
W. Hiddemann, Klinikum Grosshadern, Munich, Germany

Mantle cell lymphomas (MCL) represent a recently broadly accepted lymphoma subtype that accounts for approximately 5-8% of all lymphomas. The disease occurs in elderly patients and affects predominantly the male sex. In the pathogenesis of MCL, the translocation (t(11;14)) is thought to be of major importance. By this abnormality the Cycline D1-gene is juxtaposed to the gene of immunoglobulin heavy chain which leads to an overexpression of Cycline D1 and a deregulation of the cell cycle. Based on histology and cytology two major groups of MCL can be discriminated - typical MCL and atypical MCL of blastoid type. The latter subgroup is characterized by a high mitotic rate and Ki67 expression and frequently involves p53 mutations. The clinical course is unfavourable.

The treatment of MCL remains a dilemma in spite of numerous efforts to develop more effective and intensive regimens. A high proportion of cases respond to initial therapy with a partial or complete remission which are, however, of short duration. The median survival of patients is in the range of 3-4 years, only.

New perspectives may arise from myeloablative radiochemotherapy followed by peripheral stem cell transplantation but even more from more specific therapies such as antilymphoma immunotherapy or the application of anti bcl-1 (Anticycline D1) antisense oligonucleotides or ribozymes.
8. CNS Lymphoma

AN IN VIVO PRECLINICAL MODEL TO EVALUATE AN EFFECTIVE ANTIVIRAL REGIMEN IN EBV-ASSOCIATED PRIMARY CNS LYMPHOMA. Robert A. Baiochi, Rusoi Peng, Petra Schmalbeck, Meinl Moehsberich, Weiyan Yung, Rolf F. Barth, and Michael A. Caligiuri. The Ohio State University Comprehensive Cancer Center, Columbus, OH 43210.

Introduction: The median time of survival for AIDS patients diagnosed with primary central nervous system lymphoma (AIDS PCNSL) is less than four months despite radio- and chemotherapy and recent improvements in the suppression of HIV-1 replication. Few advances have been made in the clinical management of this EBV-associated lymphoma since its initial characterization in 1991. To the best of our knowledge, no in vivo preclinical animal model to explore novel strategies for the treatment of AIDS PCNSL has not been described.

Methods: We utilized nonocular EBV- B-cell lines derived from EBV- B-cell tumors that arose spontaneously in the setting of immune deficiency to implant into the CNS of the NIH nude rat (5 x 10^6 cells/animal). Tumor growth was followed by MRI. Animals were sacrificed after development of neurologic symptoms and pathologic examination of PCNSL tumors performed. In vitro assessment of AZT and ganciclovir (GCV)-induced apoptosis of EBV- tumors was assessed by propidium iodide and FACS. To evaluate the in vivo efficacy of antiviral treatment of EBV- PCNSL, 24 animals were implanted intracerebrally with tumor and randomized to receive: (1) PBS; (2) AZT (80 mg/kg/d); (3) GCV (60 mg/kg/d); or (4) AZT+GCV. MTX and treatment schemes of AZT/GCV were determined by dose escalation and pharmacokinetic studies, evaluating animal weight, complete blood counts, liver and renal function over a 2wk period.

Results: Stereotactic implantation allowed for reproducible delivery of EBV- tumor cells to the caudate nucleus which, after 17-21 days, resulted in expansion of the tumor and the development intracerebral seizures. Like AIDS-PCNSL, pathologic examination of PCNSL tumors from NIH nude rats revealed immunohistochemical features similar to those of AIDS PCNSL. We observed a significant improvement in survival of animals treated with AZT (mean survival time: 14.4; 1 SD = 2.8) as compared to PBS-treated mice (mean survival time: 5.8; 1 SD = 1.3). There was no difference in survival between AZT and GCV-treated animals (13.2; 1 SD = 2.5), but this 3.5x increase in survival was statistically significant (2-tail t-test, p<0.01). A combination of AZT+GCV improved survival further (15.0; 1 SD = 2.4), compared to PBS-treated mice (8.0; 1 SD = 1.4), and this difference was statistically significant (2-tail t-test, p<0.001).

Conclusions: We propose that novel therapies which target EBV- lymphoma cells in vivo can be meaningfully explored using this in vivo preclinical animal model of human EBV- PCNSL prior to clinical development in patients with AIDS PCNSL.


Maladies du Sang - Hôpital Sud - CHU Amiens - France.

GOELAMS LCP 88 trial combined 3 courses of MVBP (MTX 3 g p/m2 d1 & d3, Temozolomide 100 mg d2 & d3, BCNU 100 mg d4 & d5, Procarbazine 60 mg d4 & d5, 6 LP and a 40 Gy 'toto' cerebral irradiation). We treated 152 HIV-positive patients (pts): sex-ratio was 0.97 and median age 61 years (from 16 to 75). An obvious CR was noted in 31 pts (30%) after the first MVBP, in 69 pts (45%) after the 3rd course and in 99 pts (65%) after irradiation. In January 1999 we noted 29 relapses (from 6 to 94 months - median 16), 6 non-related deaths and 85 'specific' deaths (13 early deaths, 39 failures, 22 relapses, 10 leukemic/lymphomatos lupheas and 1 AML). The 5- and 7.5-year 'specific' survival rates are respectively 49, 36 and 29% for all the pts and 75, 55 and 49% for the 99 pts in CR.

Analysis found no prognostic value for many factors (sex, clinical data, location and number of lesions). CSF, lymphoma,...) while 3 independent factors have a strong prognostic value: age > 60 years, PS > 2 and LDH > 1000.

Factor Yes / No Survival p value
--- Age 85 / 67 pts 18 / 73 mo 2.06 x 10^-2
--- PS 85 / 62 pts 15 / 58 mo 4.0 x 10^-4
--- LDH 50 / 95 pts 13 / 56 mo 7.1 x 10^-5

We also studied the risk of occurrence of a severe neurological complication, i.e., leukencephalopathy, recurring vascular strokes, severe extra-pyramidal syndromes, above the 5% rate reported in the literature, by a factor of 3.67% for all the 152 pts. Age is an important factor while all other ones (PS, LDH, initial site, extension, CSF... ) are not significant. This risk is 48% in 11% among the 85 pts aged 60 years or more vs 25% in 5% (p = 0.03) and this risk is less than 15% for pts less than 40 years (10% 2.3%; p = 0.006). Neurologic complications will be reported by M. Gendron in another abstract.

However, when adding risks due to lymphomas and risks due to neurological complications, the prognosis of a primary central nervous system lymphoma in a patient aged less than 60 years is not bad: the 7.5-year event-free survival rate is 41 ± 8%.

PRIMARY CEREBRAL LYMPHOMAS: UNSOLVED ISSUES
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Primary central nervous system lymphomas (PCL) is a rare tumor occurring in patients (pts) without previous history of NHL and confined to the central nervous system or the eyes. It is a rare, although increasingly frequent disease, representing 1 to 2% of NHL and 5% of all brain tumors. Median age at initial diagnosis is 60 years, with a sex ratio of 1.35. Most PCL are located within the brain, or cerebellum; in rare cases, PCL present as primary leptomeningeal tumors or spinal cord lymphoma. Involvement of the eyes is observed in 20% of pts, before, synchronously, or after in most cases, PCL are diffuse large cell NHL, centroblastic or immunoblastic with a B phenotype. Diffuse small cell lymphomas, Burkitt lymphomas and T cell NHL are less frequent, but their prognosis do not appear to be different. The optimal treatment of PCL is not known. Surgery alone yields a median survival of 2 months, and is only a diagnostic procedure. In large series of pts treated with radiotherapy (RT) alone after surgery, the median survival is in the range of 12 months, with 5 years survival ranging between 9% and 29%. The RTCOG 8315 study demonstrated that even high dose (40Gy WBRT + 20Gy boost on tumor), fail to provide long term local control in most pts with PCL. Because of these poor results, chemotherapy (CT) followed or not with RT has been used in the most recent prospective studies, with apparently improved survival as compared with historical controls. However, several studies strongly suggest that the survival of these pts is improved only with drugs with a good penetration through the blood brain barrier, in particular high dose methotrexate. This is confirmed by a recently reported randomized trial comparing CHOP followed by RT vs RT alone, in which the survival of the 2 arms proved to be equivalent. In most, but not all of these studies, RT was given as consolidation treatment after CT: it is still not known whether RT should be given immediately after the end of CT or only in case of relapse. With the increasing rates of PCL, the incidence of late neurological toxicity increases. Clinical symptoms of leukencephalopathy may occur in up to 25% of pts with PCL, while CT scan or MRI alterations may be observed in up to 60% of these pts. As expected, pts at high risk are those treated with CT during or after RT, and those receiving 50 Gy to the brain or above. After CT, the optimal surveillance of pts with PCL is not known and few studies have addressed this point: in a retrospective study performed at the Centre Leon Bérard including 42 pts followed every 3 to 6 months in the first 5 years following remission, no relapse was diagnosed in a non symptomatic patient on the basis of the systematic magnetic resonance imaging of the brain in all cases. In the retrospective study performed at the Centre Leon Bérard including 42 pts followed every 3 to 6 months in the first 5 years following remission, no relapse was diagnosed in a non symptomatic patient on the basis of the systematic magnetic resonance imaging of the brain in all cases.

Introduction: Radiotherapy (RT) alone has produced uniformly poor results in primary CNS lymphoma (PCNSL). Efforts to improve on these poor results have largely been focused on the addition of methotrexate (MTX) based combination regimens. This phase 2 study aimed to assess the results of the addition of a brief course of MTX alone to cerebral irradiation.

Methods: Forty-six patients were entered from 12 Australian and New Zealand centres from 1997-1999. All were HIV negative with biopsy confirmation of the diagnosis. Median age was 58 years and 48% were ECOS PS 0-1. Three patients had positive CSF cytology at diagnosis. Treatment consisted of IV MTX (1g/m2 on D1 and 8, followed by radiotherapy on D15 (45 Gy whole brain with 5.4 Gy boost). CSF therapy using Cytosine Arabinoside via an Ommaya reservoir was only given to patients with positive CSF cytology.

Results: Forty-five of the forty-six patients completed the planned treatment, with 31 (82%) having a complete response. For all 46 patients the 2 year survival probability is 64% and median survival 33 months after a median follow-up of 33 months. As yet, however, there is no plateau on the progression-free survival curve, with 2 patients relapsing at 5 years. In total 19 patients have relapsed, with the predominant site being the brain. CSF relapse occurred in 2 patients. Neither age nor performance status impact on survival probability. Acute toxicity was generally minimal, but 1 patient died due to neutropenic sepsis following methotrexate. Late neurotoxicity has occurred in 6 patients, 4 of whom have required institutional care.

Conclusions: Brief, single agent MTX appears to improve the median survival for patients without HIV-PCNSL when added to cerebral irradiation. Late relapse in 2 patients precludes drawing conclusions about the long-term efficacy of the regimen. CSF prophylaxis is not required in the majority of patients when IV MTX doses are ≥ 1g/m2. The interaction between PCNSL and HIV is complex and detailed modality regimens in the development of late neurotoxicity remains to be elucidated.
PRIMARY CNS LYMPHOMAS (PCNSL): HIGHDOSE-CHEMOTHERAPY WITH AUTOLOGOUS PBST AND HYPERFRACTIONATED RADIOTHERAPY WITHIN FIRST-LINE TREATMENT  
Dept. of Hematology and Oncology, *Stereotaxis Neurosurgery, **Radiotherapy, ***Neuropathology, University Medical Center Freiburg, D-79106 Freiburg

Primary NHL of the CNS (PCNSL) have a dismal prognosis despite initial response to steroids or radiotherapy. Treatment with combination chemotherapy-radiotherapy (DeAngelis et al, JCO 10: 615, 1992) improves relapse free- and overall-survival but shows significant late neurotoxicity especially in patients older than 60 years, mainly due to intrathecal and post-radiation chemotherapy. Principally, high-dose methotrexate (MTX), cytoxan-arabinoside and nitrosourea are effective in treatment of PCNSL. To improve relapse-free survival and reduce neurotoxicity we initiated a pilot study in June 1997 with early-dose intensified chemotherapy with PBST followed by hyperfractionated whole-brain radiotherapy for patients aged>65. Older patients (age>65) were treated with chemotherapy based on MTX and alkylating agents without additional radiotherapy.

Induction treatment included repetitive cycles of high-dose MTX (8000mg/m²), AraC (1000mg/m²) and Thiota (40mg/m²), followed by G-CSF mobilized stem cell harvest. BCNU (400mg/m²) and Thiota (10mg/kg) were used for conditioning prior to PBSCT followed by hyperfractionated whole-brain radiotherapy (45 Gy, 2x1.5Gy/day) as consolidation. Four of six patients (age>65) showed complete remission after chemotherapy according to the protocol. No severe toxicities (WHO Grade 3 or 4) were observed, except cytopenia induced by high-dose BCNU and Thiota treatment. Two patients showed no response to initial MTX treatment and were referred to radiotherapy directly.

Six patients (age>65) were treated with following chemotherapy protocol alone: MTX (3000mg/m²), d1, d15, d30), CCNU (110mg/m², d1), Procarbazine (60mg/m², d1-10), for 3 cycles, repeated every 45 days. 3 patients showed a CR after one to three cycles, two patients are still under therapy and achieved a PR so far. Side effects included cytopenia (WHO Grade 3), one patient with severe pancytopenia due to additional hematologic toxicity died with bleeding disorder.

First-line high-dose chemotherapy produces complete remission with acceptable toxicities for patients less than 65 years of age with PCNSL. Older patients show good response to polychemotherapy alone. Both treatment regimens showed no clinical signs of neurotoxicity.

INCIDENCE AND RISK FACTORS OF CENTRAL NERVOUS SYSTEM (CNS) RELAPSE IN INTERMEDIATE-GRADE AND IMMUNOBlastic NON-HODGKIN'S LYMPHOMA (NLH) UNIFORMELY TREATED AND RECEIVING PROPHYLAXIS FOR CNS. A GELA STUDY ON 976 PATIENTS  

Introduction: CNS recurrence is an almost always fatal complication of aggressive lymphoma. The overall incidence of such an event, in some recent series of patients who did not receive CNS prophylaxis is about 5%, actually it varies from 2% to 10% according to risk groups defined on the basis of the international prognostic index (IPI) (Blood 91:1178, 1998; Ann Oncol 9:191, 1998).

Methods: In order to identify patients who deserve reinforced prophylactic treatment and those in whom prophylactic therapy might not be worthwhile we analyzed a cohort of 1373 uniformly treated adult patients under 70, enroled in two subsequent GELA trials (LNH-87 and LNH-93) between 1987 and 1988 (median follow-up: 50 months). Patients were assigned to the ACVB induction regimen (3 or 4 courses) followed by sequential consolidative treatment (LNH84 regimen). CNS prophylaxis consisted of intrathecal injections of Methotrexate performed at each cycle of ACVB and of 2 courses of high-dose intravenous Methotrexate (3g/m²) delivered at 15 days interval at the beginning of the consolidative treatment. Patients presenting with initial meningeal localisation were excluded.

Results: 976 patients in complete remission were analyzed. The main initial characteristics of these patients are: NHL histologic types 77%, T-cell phenotype 19%, LOH >1N: 35%, 11q14 stage: 62%, ECCO<1: 15%, EN sites >1: 28%, BM involvement 10%. The risk retparation on the basis of IPI is low (L): 42%, low-intermediate (LI): 27%, high-intermediate (HI): 19%, high (H): 12%. The overall incidence of CNS relapse is 2,5% (n=24), either isolated (1,7%) or associated with diffuse disease (0,8%). In univariate analysis, an increased risk for CNS recurrence is associated with male sex (p=0.04), pleural localization (p=0.005), EN sites >1 (p=0.001), testis localization (p=0.001), IPI (p=0.03) and LOH>1N (p=0.05). Multivariate logistic regression analysis identifies male sex (p=0.002), RR = 4.6), testis localization (p=0.003), RR = 10.8) and IPI (p=0.03, RR = 2.8) as independent predictive factors. Thus, IPI divides our population in two risk groups who significantly differ for occurrence of CNS relapse (L-1 risk groups: 1% vs H-1 risk groups: 4.7%).

Conclusions: We conclude that a CNS prophylaxis notably reduces the risk of CNS relapse in higher risk patients as compared to the recently reported risk for such patients who did not receive prophylaxis. A reinforced prophylactic treatment using drugs that cross the blood-brain barrier remains to be considered to further decrease this risk. By contrast, no benefit of such a prophylaxis is observed in our lower risk group for whom a reduction of prophylactic treatment, especially intrathecal injections, should be envisaged.
9. High Dose Chemotherapy in Multiple Myeloma

TANDEM TRANSPLANTS (TAT) in OVER 1,000 PATIENTS WITH MULTIPLE MYELOMA (MM)
- INFERRIOR PROGNOSIS WITH CHROMOSOME 13 DELETION. B Barlogie, R Denihan, D Spoon, J Gaynor, I Shemesh, M Doshi, J Singshal, N Mchael, N McNeil, and E Alexander
- University of Arkansas for Medical Sciences/Arkansas Cancer Research Center, Little Rock, AR.

Since 1980, 1,051 pts were enrolled in TAT trials employing melphalan 200mg/m². 60% were older than age 50, 43% and 50% had elevations penta-TAT of BM<25% and CRP>4.0, respectively. 40% had more than 15 mos of prior therapy. 40% achieved CR and median CR duration was 2.4 yrs. Median duration of event-free survival (EFS) and overall survival (OS) were 1.9 and 3.5 yrs, respectively. Multivariate analysis of pre-TAT standard variables identified low levels of BMG and CRP as well as ≥12 mos of prior therapy as the most important independent favorable parameters associated with extended EFS and OS. The recently recognized prognostic importance of del 13 among newly diagnosed patients was confirmed in this large group comprising also previously treated patients. Indeed, among the 564 pts with ≥12 mos, 176 pts with >12 to 24 mos and 208 yrs with <24 mos (with all data available), approximately 25% in each of these 3 groups had del 13 whose EFS and OS was significantly longer (p=0.05) compared to the remaining 75% lacking this cytogenetic feature (p=0.01). Similarly, when patients were classified by the number of favorable variables present (low BMG, low CRP and ≥12 mos of prior therapy), the presence of del 13 identified a high risk subset within the 4 groups displaying 2, 3, 4 or 0 favorable variables. When del 13 was included in the multinomial analysis of pre-TAT factors, its presence was a dominant feature for extending EFS and OS (HR of 40.47) along with BMG ≤2.5 (HR of 2.03) and ≥12 mos of prior therapy (HR of 6.47) and BMG ≥2.5 (HR of 7.35-8.46) (all with p<0.005). These data support the recent observation that del 13 represents a key adverse prognostic feature among other standard factors, justifying, to our knowledge, assessment in all patients with MM which can be conveniently performed by transplant FISH analysis of RB-1 and other chromosome 13 probes.

** Number of Favorable Factors**

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<th>p-value</th>
<th>OS**</th>
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*BMG≤2.5, CRP≤4.0, prior therapy ≥12 months
** Median years

THE ROLE OF HIGH-DOSE CHEMOTHERAPY IN THE TREATMENT OF MULTIPLE MYELOMA—A CONTROVERSY

ROBERT A. KYLE, M.D.

Most patients with multiple myeloma have symptomatic disease at diagnosis and require therapy. Patients with smoldering multiple myeloma should not be treated because they may remain stable for long periods of time. If the patient is younger than 70 years, the physician should consider the possibility of an autologous peripheral blood stem cell transplant. Ideally, this should be done as part of a prospective study. Hematopoietic stem cells are damaged by alkylating agents so they must be collected before these agents are given. Autologous stem cell transplantation does not induce a cure and most patients will relapse. The appropriate timing of an autologous stem cell transplant has not been ascertained. The advantage of immediate transplant following stem cell collection is that the inconvenience, cost, and potential complications from chemotherapy are eliminated. In contrast, a transplant following relapse after successful chemotherapy may not be necessary for a number of years and the morbidity and mortality of the procedure is delayed and its effectiveness may be enhanced. Hopefully, better preparative regimens and the removal of contaminated tumor cells from the peripheral blood may make the transplant more effective.

Another major question is whether double (tandem) transplants are superior to a single autologous stem cell transplant. A recent French Myeloma Group Study should answer this question. Allogeneic transplantation for multiple myeloma must be made safer because the transplant-related mortality is 40%-50%. The depletion of T-cells may reduce transplant-related mortality. The relapse of multiple myeloma following allogeneic transplant is a major problem and consequently the preparative regimens must be improved. The infusion of donor lymphocytes following an allogeneic transplant is useful. New approaches using immunologic aspects including the use of dendritic cells and vaccines are of potential importance for the future.
10. Biology III

EPIEMIOLOGY OF NON-HODGKIN'S LYMPHOMA: REVIEW AND RESEARCH AGENDA
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The incidence of non-Hodgkin's lymphoma (NHL) has increased 85% over the past 22 years in the United States, with similar increases observed in other countries around the world. AIDS-related lymphoma and diagnostic changes do not appear to explain the trends. Other acquired and genetic immunodeficiency states are associated with extremely high risks of NHL, but their prevalence rates have not changed dramatically or are too low to explain the widespread increase in the general population. Rather, the rising incidence suggests the presence of an etiologic agent increasing in prevalence in the general environment. Recent research has identified several possible candidates including pesticides, other organochlorine compounds, solvents, drinking water nitrates, sunlight, and hair dyes. There is an urgent need to evaluate whether these common exposures are contributing to the rapid rise in NHL, and to investigate other hypothesized risk factors such as viruses, medical conditions, medical treatments, and genetic factors. Two multidisciplinary population-based case-control studies have been launched recently in the U.S. to examine the impact on NHL risk of these important environmental, occupational, viral, medical, and personal exposures. Similar studies examining some of the same hypotheses are also underway in Europe. Study methods will be described, including innovative methods to assess pesticide exposure in the home, nitrates in drinking water, and hair dye use, as well as biological specimen collection for measurement of compounds in the serum and urine, antibodies to viruses, and examination of genetic polymorphisms.

TRANSLATION 14(18) IN HEALTHY INDIVIDUALS: ASSOCIATION WITH FAMILY HISTORY AND AGRICULTURAL EXPOSURE
O. Patiel, L. Gordon, A. Zeelenber, I. Sverdlin and D. Ben-Yehuda, Dept of Social Medicine and Hematology, Hadassah Medical Center, Jerusalem, Israel and Memorial Sloan Kettering Hospital, New York, NY.

The t(14;18) translocation, present on 90% of follicular and 25% of diffuse large cell non-Hodgkin's lymphomas (NHL), has been found in low levels in healthy persons. Its clinical/prognostic significance in healthy populations is unknown, and risk factors for its development have not been determined.

Objectives: To assess the prevalence of t(14;18) in individuals without NHL, comparing city dwellers with residents of agricultural settlements (kibbutzim), as well as first-degree relatives of NHL cases.

Methods: Residents of kibbutzim were interviewed extensively about exposures and had blood drawn for t(14;18) determination. Two control groups: 1) Jerusalem residents- randomly selected hospital administrative workers and 2) 1st degree family members of NHL patients were interviewed and tested. The translocation was detected after B cell purification of blood samples using UNI-SORB (Eldan-Tech Ltd, Jerusalem, Israel) using rested PCR. The method detects the translocation in a BCL2 positive cell line after dilutions of up to 1:100 with normal peripheral blood lymphocytes.

Results: 13 of 197 healthy individuals (6.6%) tested positive for t(14;18). No statistically significant differences in t(14;18) prevalence were detected between the rural and urban populations. However, all t(14;18) positive subjects reported previous agricultural residence for at least one year since the age of 18. No age or sex differences between t(14;18) positive and negative individuals were found. No significant association between exposure to specific agricultural or other chemicals was found.

<table>
<thead>
<tr>
<th>Group</th>
<th>Urban</th>
<th>Kibbutz</th>
<th>1st degree relatives</th>
<th>Total</th>
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<tr>
<td>t(14;18)</td>
<td>1 (1.1%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (0.6%)</td>
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<tr>
<td>t(14;18) total</td>
<td>32</td>
<td>135</td>
<td>35</td>
<td>192</td>
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</table>

Conclusions: The presence of the t(14;18) translocation in healthy individuals was not associated with current agricultural residence in this preliminary study. Whether relatives of patients with NHL are at increased risk requires further study in larger populations. Specific exposures affecting the onset of this translocation have not been ruled out. The significance of this translocation in healthy individuals remains unknown.

NON-HODGKIN'S LYMPHOMA AND OCCUPATIONAL EXPOSURE TO CHEMICALS IN CANADA
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Introduction: The incidence of non-Hodgkin’s Lymphoma (NHL) has increased dramatically in Canada over the past 20 years. The etiology of NHL is poorly understood. The purpose of our study was to assess the effect of occupational exposure to specific chemicals on the risk of NHL.

Methods: Mailed questionnaires were used to obtain data on 1464 newly diagnosed histologically confirmed NHL cases and 5075 population controls between 1994 and 1997 in eight provinces of Canada. Data were collected on socioeconomic status, lifestyle, diet, occupation, years of exposure to any of 17 chemicals. Odds Ratios (OR) and 95% confidence intervals (CI) were derived by logistic regression.

Results: The study found an increased risk of NHL among males exposed to benzidine, mineral, cutting or lubricating oil, pesticides and herbicides. Compared with non-exposure to specific chemical, the adjusted ORs were 1.92 (95% CI = 1.09-3.77) for benzidine, 1.24 (95% CI = 1.01-1.53) for mineral, cutting or lubricating oil, 1.28 (95% CI = 1.00-1.64) for herbicides and 1.27 (95% CI = 1.01-1.60) for pesticides. Excess risk of NHL was associated with exposure to pesticides and wood dust among females. The adjusted ORs were 1.44 (95% CI = 1.03-2.00) for wood dust and 1.40 (95% CI = 0.99-1.88) for pesticides. The ORs increased with increasing exposure in years to pesticides and herbicides for males, and with increasing exposure years to wood dust for females. These trends were statistically significant (p<0.05).

Conclusions: The findings in this study suggest that occupational exposure to specific chemicals plays an important role in the development of NHL in Canada.

Does a T-cell type of Hodgkin Lymphoma exist?
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Introduction: There are two biologic entities in Hodgkin lymphoma (HL): lymphocyte predominance HL (LPHL) and classic HL comprising nodular sclerosing, mixed cellular, lymphocyte rich and lymphocyte depleted variants. Recent single cell molecular studies have shown that LPHL is a clonal B-cell neoplasm in 100% of cases, and classic HL in 85-95% of cases. Attempts to clarify the origin and nature of the Reed-Sternberg (RS) of the remaining cases of classic HL have so far failed. However, data obtained from cell lines as well as from immunostained tissue sections suggest that the RS cells of the remaining cases could be related to T-cells.

Methods: We isolated single RS cells from histological sections of fourteen cases of classic HL which expressed T-cell characteristic antigens and of six cases of null-cell phenotype. The RS cells were analyzed for their T-cell receptor gamma (TCR gamma) gene configuration by single copy PCR. Six of the classical HL with a T-cell phenotype were also analyzed for the presence of immunoglobulin (lg) heavy and light chain rearrangements.

Results. Only two of the fourteen classic HL cases with a T-cell phenotype and none of the null-phenotype carried monoclonal TCR gamma gene rearrangements. To determine whether the RS cells of the remaining cases with a T-cell phenotype are genetically related to B-cells or other cells, we investigated their Ig gene rearrangements. The RS cells of all these cases were shown to harbor clonal Ig gene rearrangements.

Conclusions. Classic HL of T-cell type really exists although they are very rare. A surprising finding was that most classic HL cases with a T cell immunophenotype are of B-cell origin.
APOPTOSIS AND CHEMOTHERAPY OF MALIGNANT TUMORS

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APO-1 (Fas/CD95), a member of the tumor necrosis factor (TNF) receptor superfamily induces apoptosis upon receptor oligomerization. The receptor and its ligand are important for apoptosis of peripheral T cells, for downregulation of an immune response and most likely, at least in part, also for peripheral T cell tolerance. In Aids, apoptosis mediated by this system might contribute to the depletion of T helper lymphocytes.

In a search to identify intracellular signalling molecules coupling to oligomerized APO-1 several cytotoxicity-dependent ΔAPO-1-associated proteins (CAP) were immunoprecipitated from the apoptosis-sensitive human leukemic T cell line IUT 78 and the lymphoblastoid B cell line SKW6.4. CAP1-3 and CAP4 instantly detectable after crosslinking of APO-1 were only associated with aggregated and not with monomeric APO-1. CAP1 and CAP2 were identified as phosphorylated MORT1 (FADD) (Boldin, M.P., Varfolomeev, E.E., Pancer, Z., Mett, I.L., Camonis, J.H. and Wallach, D. (1995) J. Biol Chem 270, 7795-7798; Chinnaiyan, A.M., O’Rourke, K., Tewari, M. and Dixit, V.M. (1995) Cell 81, 505-512.). Association of CAP1-4 with APO-1 was not observed with C-terminally truncated non-signalling APO-1. CAP1 and 2 did not also associate with an APO-1 cytoplasmic tail carrying the Δp55 amino acid replacement. CAP1-4 form a death-inducing signalling complex (DISC) with the APO-1 receptor and are, thus, the first APO-1 associating proteins of a signalling cascade mediating apoptosis. Recently CAP4 was characterized and named FLICE (caspase 8a and 8b).

FLICE is a zymogen and converted into an active protease at the DISC. FLICE is an essential signalling molecule that also plays an important role in execution of apoptosis in chemotherapy. Furthermore, induction of apoptosis in chemotherapy in several tumors involves upregulation of the APO-1 death system and is dependent on intact p53.

18 FDG-PET FOR ASSESSMENT OF RESIDUAL MASSES ON CT AFTER TREATMENT OF LYMPHOMAS

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Introduction: The problem of residual masses on post-treatment CT scans is a continuing dilemma for the oncologist treating malignant lymphomas. These residual masses may contain active disease or represent only necrotic tumour which continues to shrink without further treatment or post treatment fibrosis which remains stable on continued follow-up. 18-FDG-PET offers a novel metabolic imaging modality which can differentiate malignant from benign tissue on the basis of increased glycolytic activity.

Methods: Thirty-two patients (15 with Hodgkin’s Disease and 17 with aggressive histology Non-Hodgkin’s Lymphoma) who had residual masses on their post-treatment CT scans underwent 18-FDG-PET. The post-treatment CT and PET scans were compared and the accuracy of the 18-FDG-PET scan in assessing residual masses was evaluated using clinical and pathological follow-up data.

Results: Nine patients had positive post-treatment 18-FDG-PET, 8 (89%) of whom have relapsed. Twenty-three patients had negative post-treatment PET with only 2 (9%) relapses in this group. The 2 patients who relapsed had aggressive NHL, while none of the 11 HD patients who had negative PET relapsed. The median follow-up is 31 months.

Conclusions: 18-FDG-PET can differentiate, with a high degree of accuracy, between residual masses containing viable tumour where further treatment will be required to achieve cure and those representing ablated disease, where unnecessary treatment and additional morbidity may be avoided.
EORTC CLASSIFICATION FOR PRIMARY CUTANEOUS LYMPHOMAS

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In 1997 the EORTC Cutaneous Lymphoma Group proposed a new classification for the group of primary cutaneous lymphomas (Blood, 1997; 90: 354-371). This EORTC classification is the first classification, which is designed exclusively for the group of primary cutaneous lymphomas. It is also the only classification, which is not only based on histological criteria, but consistently takes into account clinical criteria as well. It contains a limited number of well-defined types of cutaneous T-cell lymphomas (CTCL) and cutaneous B-cell lymphomas (CBCL), which together comprise more than 90% of all primary cutaneous lymphomas. In addition, it contains few provisional entities, which mostly display characteristic histologic features, but of which a distinctive clinical presentation and/or clinical outcome have not yet been defined. The clinical significance of the EORTC classification has now been validated by two large studies including almost 1000 primary cutaneous lymphomas. The EORTC classification is not just a new classification, but represents a novel approach in the diagnosis and classification of cutaneous lymphomas. For clinicians, the EORTC classification has the great advantage that it provides detailed information regarding the management, treatment and prognosis of the disease entities included. For pathologists, usage of a classification which is not only based on histological criteria, but takes into account clinical criteria as well, is much more difficult, as it implies that the histologic diagnosis is not always the final diagnosis, and can not be used as a basis for therapy. Crossover talk between the pathologist and the clinician is essential to arrive at a definite diagnosis.

The aim of this presentation is to illustrate the basis principles of this new classification. In addition, the relationship between the EORTC REAL and the forthcoming WHO classification will be discussed.

11. Cutaneous Lymphoma

The principles of the REAL-classification have been adopted by the WHO committees for the classification of hematopoietic and lymphoid neoplasms. Each disease is defined as a distinct entity based on an integration of morphology, immunophenotypic and genetic features, clinical presentation and course, and normal cellular counterpart. If either primary or secondary involvement of the skin is a constant factor, this aspect is considered integral to disease definition. Organ-specific classification schemes, such as the EORTC classification for cutaneous lymphomas, are not required, and indeed may impede the recognition of common features of diseases involving multiple anatomic sites. For example, cutaneous marginal zone B-cell lymphomas (formerly designated cutaneous immunocytomas) mirror the features of MALT lymphomas in other anatomic sites. While we recognize that the EORTC classification for cutaneous lymphomas attempts to emphasize certain aspects of these neoplasms of importance to dermatologists, the use of multiple classification systems is a step backward, and may lead to confusion among hematologists/oncologists, and dermatologists.

Nevertheless, cutaneous lymphomas in many instances are distinct. Their natural history is often more indolent than nodal lymphomas, and for that reason they often require different therapeutic approaches. We agree with the efforts of the EORTC classification to emphasize the unique clinical aspects of many cutaneous lymphomas, as this recognition is essential for appropriate clinical management. As has been learned for nodal lymphomas, clinical features play an important role in prognosis and should be utilized in guiding therapy. For cutaneous lymphomas, the presence or absence of systemic spread is particularly important.

Clinical Approach to B-cell and T-cell Cutaneous Lymphomas

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Cutaneous B-cell lymphomas (usually diffuse large cell) and mycosis fungoides (MF, a T-cell lymphoma) account for the majority of cutaneous lymphomas. Less common types include CD 30+ anaplastic large cell and CD56+ NK-cell lymphomas. Plts with cutaneous B cell lymphoma undergo routine lymphoma staging. Stage IE disease is often treated successfully with localized irradiation (35-45 Gy, depending on histology). Chemotherapy may be reserved as a salvage treatment (Rx). For Stage IIE-IV, skin involvement is often incidentally and the type of Rx is mandated by the histology and overall stage. MF is generally diagnosed in the limited (T1) or generalized (T2) plaque phase of skin involvement. Staging studies need only include chest radiography, blood counts, and a Zezera prep. In T1-2 disease, extracutaneous disease is rarely evident. Simple topical therapies such as topical nitrogen mustard and PUVA often provide excellent control of disease. A small percentage (~20-25%) of pts with T1 disease may be free from disease recurrence after a single course of Rx. Most pts will experience recurrence of disease and require intermittent Rx for many yrs. Pts with T1 disease will not have a compromised life expectancy. Adjunct chemotherapy provides no benefit for patients with early stage disease. Pts with progressive generalized plaque disease (T2) or tumorous involvement (T3) are at higher risk for developing extracutaneous disease. Suspicious lymphadenopathy should be biopsied. Control of skin disease in these pts is achieved most readily with topical skin electron beam therapy. Adjunct Rx with topical nitrogen mustard or PUVA may improve the duration of control. Nodal sites of extracutaneous disease may be palliated effectively with irradiation, but visceral disease managed by so-called systemic Rx. Unfortunately, conventional chemotherapy generally only achieves partial and/or brief responses. Interferon achieves good responses in some patients with advanced disease and investigational therapies are justifiable in these high risk patients. Pts with erythroderma (T4) are challenging to treat. If there is no extracutaneous disease and limited peripheral blood involvement, PUVA or extracorporeal photopheresis +/- interferon may be used as primary therapy. Patients with the Sezary syndrome (T4, adenopathy, and circulating Sezary cells) usually require systemic management. Independent prognostic factors in T4 disease include age (<50 vs. >50), extracutaneous disease (T1-2 vs. T3-4), peripheral blood involvement (<5% vs. >5% of lymphocytes). Ten-year survivals for T1, T2, T3, and T4 are 90%, 60%, 25%, and 30%, respectively.
A DERMATOLOGIST'S APPROACH TO THERAPY FOR CTCL
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Cutaneous T Cell Lymphomas include Mycosis Fungoides (MF) & Sezary Syndrome (SS). These present to the Dermatologist as either chronic eczematous or poikilodermatous dermatitis and share with them many clinical and immunologic features as well as response to therapy. MF/SS are distinguished by epidermotropism and by clonal or oligoclonal proliferation of CD4+ memory T cells. Like other T cell mediated skin diseases there is an HLA Class 2 association, suggesting the clones are antigen or superantigen driven, possibly by staphylococcus in a subset of patients. Since these are by and large indolent lymphomas in which chemotherapy does not prolong survival, the first goal in therapy of CTCL is to eliminate putative antigens, and to create an inhospitable skin environment for T cell proliferation. The second major goal is to selectively eliminate T cell clones rather than use blunt force therapy. Since early stage patients have a benign chronic course, therapies should be conservative and directed to skin and include topical steroids, retinoids or topical chemotherapy, phototherapy, and radiation, and low dose methotrexate. Cytokine therapy with interferon or interleukin 12 alone or in combination with oral retinoids or phototherapy are also attractive alternatives. Targretin is an RXR selective retinoid with activity in refractory CTCL. These therapies preserve the immune system and health of the patient and offer control of this chronic skin disease for many years. Other T cell targeted approaches include the IL-2 fusion protein (DAB401-IL2, Ontak) which is specific for CD25+ activated T cells. Ontak is especially helpful in patients who are stage IIIB with an overall response rate of 30 %. Agents that interfere with T cell growth include Pelidesine (Bcx34) and nucleoside analogues, Pentastatin and Cladribine. The latter two may create long-term immunosuppression. Sezary patients may have increased survival and response to photopheresis therapy, alone or in combination with interferon. Photopheresis may work by providing T cell vaccination. DNA vaccination against specific Vb regions of T cell clones would offer an advance in the treatment of early MF. Treatment of early stage patients with agents targeting the clonal T cell response should help increase survival and preserve immune function.

An Oncologist's approach to Therapy for Cutaneous T-Cell Lymphoma (CTCL)
F. Foss, MD
Tufts New England Medical Center, Boston, Massachusetts USA

CTCL comprises a heterogeneous group of diseases manifested in many cases by a prolonged clinical course. At the onset, even patients with advanced clinical disease, including erythroderma, adenopathy, and cutaneous tumors, can respond to a number of conservative therapeutic modalities, including radiation, cutaneous and extracorporeal photopheresis, and interferon. More aggressive systemic therapies are generally reserved for patients with visceral involvement, effaced (LN4) lymph node disease, or patients refractory to multiple conservative approaches. Since no survival benefit has been demonstrated for multi-agent cytotoxic chemotherapy regimens, this therapy is generally reserved for patients whose disease demonstrates an aggressive clinical course requiring immediate palliation. Durable responses (>5 years) have been reported with purine analogs, however prolonged immunosuppression and increased frequency of opportunistic infections has been demonstrated. Novel therapeutic agents, including IL2, IL12, the phosphorylase inhibitor, BCX-34, Targretin have demonstrated activity. The IL2 diphtheria toxin fusion protein, ONTAK, has demonstrated a 30% response rate in advanced and refractory CTCL patients. The optimal role of targeted biological therapies in advanced patients will likely be in the minimal disease setting following either chemotherapy or radiation.
Regulators of apoptosis in B-cell neoplasms

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Defects in programmed cell death mechanisms contribute to the pathogenesis of many non-Hodgkin's lymphomas, and also underlie intrinsic mechanisms of chemoresistance and radioresistance. Several apoptosis-regulatory proteins have been identified and efforts are underway to delineate the mechanisms by which they exert their influence on cell life and death.

Members of the TNF family of cytokine receptors play major roles in controlling the proliferation and survival of lymphocytes. The receptors for TNFα, Fas, TRAIL, and related proteins trigger activation of caspase-family cell death protein through a mechanism involving recruitment of proforms of certain caspases to receptor complexes. In contrast, CD40 and some other TNF-family receptors provide signals for cell survival, often as a result of NFκB activation—which in turn stimulates the transcription of several anti-apoptotic genes, including Bcl-xL, Mcl-1, and cIAP2. The balance between the activities of the death-inducing and survival-promoting TNF-family cytokine receptors may be upset in lymphomas. In some B-cell malignancies, for instance, CD40 upregulates expression of Fasl, an anti-apoptotic protein that binds pro-caspase-8, preventing recruitment of caspase-8 to Fas receptor complexes and suppressing Fas-induced apoptosis. We have also identified other modulators of the TNFR and Fas pathways for apoptosis, including (a) IκBα, which binds caspase-8 and (b) BAG1 (SODD), which may bind the intracellular death domain region of TNFR1. Overexpression of these proteins occurs in some types of cancer, suggesting additional aberrant mechanisms for suppression of Fas/TNF-mediated apoptosis.

Mitochondria play important roles in apoptosis regulation, releasing caspase-activating proteins into the cytosol, including cytochrome c. Cytochrome c binds to Apaf-1 in the cytosol, resulting in formation of Apaf-1/caspase-9 complexes and triggering caspase-9 activation. We have observed that growth factors and certain oncogenes which provide signals for cell survival can regulate the relative sensitivity of cells to cytochrome c-mediated caspase activation by controlling phosphorylation of caspases within this pathway. Over-expression of IAP-family anti-apoptotic proteins can also hinder signaling through the cytochrome c pathway. IAPs directly bind to and inhibit selected caspases, including caspase-9, thus suppressing apoptosis. In contrast, anti-apoptotic Bcl-2 family proteins such as Bcl-2 and Bcl-xL integrate into mitochondrial membranes and prevent release of cytochrome c, thus functioning upstream of caspases within this mitochondrial pathway for cell death.

Understanding the mechanisms of apoptosis regulation in normal and malignant B-cells is beginning to suggest strategies for promoting apoptosis and enhancing chemoresponses of non-Hodgkin's lymphomas.
DOSE ESCALATED BEACOPP CHEMOTHERAPY FOR ADVANCED HODGKIN'S DISEASE: PROMISING RESULTS OF THE FOURTH INTERIM ANALYSIS OF THE HD9 TRIAL


Introduction: The HD9 trial aimed to assess the effect of increased drug dose on efficacy and toxicity in the BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) regimen in advanced stage Hodgkin's disease (HD).

Methods: Patients (pts.) between 15 and 65 years, either in stage IIIA/IIIA with risk factors or in stages IIIIB/IV, were eligible. Eight courses of chemotherapy were followed by irradiation of initial bulky and residual disease. From 2/93 to 4/94, 1200 pts. were randomized between COPP/ABVD (arm A), BEACOPP baseline dose (arm B) and BEACOPP escalated dose (arm C). Baseline BEACOPP was approximately equivalent to COPP/ABVD but shortened to a 3 week course. Cyclophosphamide, etoposide and doxorubicin were escalated to 1920, 2000 and 1400 mg/m² respectively, and G-CSF was administered in arm C from day 8 until leukemia recovery. Results: Results of the fourth interim analysis (1999) will be presented, with over 1000 evaluable pts. and a median observation time of 30 months. A preliminary analysis suggests that BEACOPP PM remains significantly superior to COPP/ABVD at all time points. Further, comparison of arms B and C shows that progression rates during treatment and freedom from treatment failure (PFF) are both significantly improved due to escalation. Acute toxicities (neutropenia, thrombocytopenia, anemia, infection) were similar in arms A and B, in arm C they were increased but manageable; toxic deaths were not more frequent than for COPP/ABVD. Second coagulopathy (analysed 11/98) occurred in arm A in 8 pts. (no AML, 6 NHL, 2 solid tumours (ST)), arm B 6 pts. (1 AML, 4 NHL, 1 ST) and arm C 5 pts. (5 AML, 1 NHL, 0 ST). Conclusions: We conclude that dose escalation is feasible and increases efficacy. Leukemogenesis must be further monitored.

Intensive Therapy With Autologous Stem Cell Support (ABMT) For Relapsed or Refractory Hodgkin's Disease (HD): Long-term Follow-up and Late Events

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Introduction: We have previously shown that disease status at time of ABMT is the most important factor determining DFS in patients (pts) with relapsed or refractory HD (J Clin Oncol 1993); we now present 10 year follow-up and survival data.

Methods: 194 pts with relapsed/refractory HD after MOPP-ABVD/ABVD chemotherapy were treated to maximum response with salvage chemotherapy (+ XRT to prior sites of bulky disease), followed by toposide 60 mg/kg + melphalan 160 mg/m² and ABMT. Pt characteristics: median age 31y (R 16-61), 62% male. B symptoms 49%, relapse in radiation field 31%, 10% were refractory to initial chemotherapy, 37% had CRI < 1 yr, 41% CRI > 1 yr. At ABMT, 40% had CR with salvage therapy and 60% PR.

Results: Median follow-up is 5 yrs (R 0.5-10). 100 day mortality was 5.6%. There have been 77 relapses (40%); median TTR 8 mos (R 1-58 mos). Event-free survival (EFS) is 40% at 5 yrs and 28% at 10 yrs; overall survival (OS) is 48% and 30% and is similar in pts with CR1 or -1 yrs. Pts transplanted in CR had superior EFS (42 vs 20% and OS (48 vs 18%) compared to those in CR (p<0.001 for both comparisons) and in multivariate analysis, disease status at BMT (CR vs PR) was the only significant predictor of outcome. Eight deaths occurred ≥5 yrs post-ABMT: complications of hepatitis/liver transplant (2), AML (1), lung cancer (1), allogeneic BMT (1), unexplained death (1). HD ABMT: A RANDOMIZED STUDY FROM 4 cases of 2 AML and 2 B MDS (actuarial incidence 11% at 6 yrs).

Conclusions: Late non-relapse events contribute substantially to mortality in pts with relapsed HD receiving ABMT. EFS is 30% at 10 years but there is no evidence of a plateau in EFS or OS in this patient population. Pts receiving ABMT in CR after salvage chemo continue to have superior survival.
Department of Haematology, S.Martino Hospital, Genova, Italy.

Introduction: The aim of this multi-center study was to compare the effectiveness of conventional treatment with high-dose therapy (HDT) plus ASCT in improving survival and DFS of 1st remission adult LBL patients.

Methods: From November 1992 to April 1997, 119 adult pts with LBL from 33 European centres entered the EBMT/UKLG LY01 study. All pts were treated with standard remission induction therapy. Responding pts were randomized to either conventional dose consolidation/maintenance therapy (CT) or HDT and ASCT. In some centres, pts with HLA-identical sibling donors were registered, but proceeded to allogenic BMT without randomisation. Randomised pts who had relapsed after CT but who responded to salvage therapy received ASCT in 2nd remission. Pt characteristics: Male 83, female 36; median age 26 years (range 14 to 65); Ann Arbor stage III/IV 83, T cell 80; LDH elevation 64. Results: Response to induction therapy: CR 67 (56%), PR 31, NR/PD 9; toxic death 1; protocol violation 1; inevitable 7. Sixty-five pts were randomised (31 ASCT, 34 CT). Reasons for failure to randomise: NR/PD 16; toxicity of induction therapy 5; allogenic BMT 12; protocol violation 6; patient refusal 12. For randomised pts, the 3yr actuarial relapse free survival is 56% in the ASCT arm, versus 14% in the CT arm (p=0.08). Corresponding 3yr actuarial overall survivals are 62% and 52% respectively (p=0.98).

Conclusions: These results suggest that ASCT is superior to conventional dose chemotherapy as post-remission therapy for adult LBL. The fact that overall survival is the same for both arms may reflect the effectiveness of ASCT in 2nd remission for patients who relapse after conventional consolidation therapy.

The British National Lymphoma Investigation, Department of Haematology and Oncology, University College London Medical School, (UCLM), London, W1N 8AA.

Methods: Between November 1987 and October 1992, 471 patients aged between 16 and 69 years with untreated histologically aggressive NHL with a large cell component were entered into a randomized trial of CHOP vs PACEBOM a weekly 7 drug regimen containing etoposide. 12 patients were excluded after histological review. The initial results on the remaining 459 patients were published in 1996 and showed no significant difference between the two regimens.

Results: A further 4 years follow up is now available and the results are tabulated below.

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<th>CHOP</th>
<th>PACEBOM</th>
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<tr>
<td>Complete remission</td>
<td>57%</td>
<td>64%</td>
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<tr>
<td>CR-relapse free survival at 8 years</td>
<td>60%</td>
<td>65%</td>
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<tr>
<td>Cause specific survival at 8 years</td>
<td>52%</td>
<td>63%</td>
</tr>
<tr>
<td>Overall survival at 8 years</td>
<td>41%</td>
<td>51%</td>
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There have been 13 second malignancies in the CHOP arm and 6 in the PACEBOM arm (difference not significant). A subgroup analysis for cause specific survival indicated that the major benefit for PACEBOM occurred in patients with stage IV disease. In such patients the actuarial cause specific survival at 8 years was 54% in the PACEBOM arm versus 35% in the CHOP arm (p=0.03). The overall survival in these patients was 41% and 26% (p=0.06).

Conclusions: These data suggest that multiagent weekly regimens with a high relative dose intensity may merit further exploration in patients with very advanced disease.

8-WEEK VNCOP-B VERSUS 12-WEEK VNCOP-B IN ELDERLY PATIENTS WITH HIGH GRADE NON-HODGKIN'S LYMPHOMA (HG-NHL), PRELIMINARY RESULTS FROM AN ONGOING PROSPECTIVE RANDOMIZED CLINICAL TRIAL.
F. Ghelizzi, on behalf of an Italian Cooperative Study Group on malignant lymphomas.
Institute of Hematology and Medical Oncology "L. e A. Seraglioni", University of Bologna, Italy.

Introduction: Age has been recognized as the major prognostic variable in patients (pts) with HG-NHL. In the last years, numerous chemotherapy regimens specific for elderly pts have been devised. We recently reported (ICO, 89: 3974, 1997) that a 8-week MACOP-B-like scheme, VNCOP-B, is feasible and effective in elderly HG-NHL pts, and that the use of G-CSF reduces significantly infection and neutropenia rates. The purpose of this randomized study was to evaluate whether the addition of 4 more weeks of therapy to standard 8-week VNCOP-B could improve clinical results in terms of complete remission (CR) rate, overall survival (OS) and relapse-free survival (RFS), without modifying the incidence of toxic events.

Methods: Since March 1996, 226 previously untreated HG-NHL, aging 60 years and older, coming from 22 Italian institutions, were randomized to receive either 8-week VNCOP-B (group A) or 12-week VNCOP-B (group B). Randomization was 1:1. G-CSF was administered subcutaneously in all pts, starting on day 2 of every week for 5 consecutive days. The two groups are fully comparable in terms of clinical and pathologic features. Median age is 69.8 years.

Results: Median follow-up is 13 months. CR rates are 54% in arm A and 59% in arm B, and did not differ between pts aged less or more than 70 years. 17% of complete responders in arm B relapsed, versus 23% in arm A. In arm A, 7% of the pts died from causes unrelated to NHL, compared to 5% in arm B. No differences were recorded in terms of number of pts with at least one toxic events of any WHO grade (73%), or at least one grade III-IV toxic event (46%). Hospitalization rate was the same in the two groups (11%). 3-yrs projected OS is 61% in arm A and 62% in arm B. International Prognostic Index was significantly associated with the outcome (p=0.000000) in both arms.

Conclusions: These preliminary data suggest that the addition of 4 more weekly drug administrations to standard 8-week VNCOP-B does not translate into a better response to treatment, nor into higher toxic effects.