Abstracts of Satellite Symposium

Baxter Oncology GmbH, Tuesday, June 11, 2002, Room B1, 07:30 p.m.
Advances in the Management of Relapsed Aggressive Non-Hodgkin Lymphoma and Hodgkin's Disease

EUROPEAN EXPERIENCE IN THE TREATMENT OF RELAPSED AGGRESSIVE NON HODGKIN (NHL) AND HODGKIN'S LYMPHOMA (HL).
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Salvage regimens for relapsing patients with lymphoma generally include different drugs in order to avoid cross-resistant association and cumulative toxicity. Investigators had focus in Europe to the search of alternative combination to the classical DHAP, expecting a better response rate and better eligibility to transplant. In NHL most of the regimens were combination with Ifosfamide-Etoposide. When associated with Ara-c and Methotrexate (IVAM), it provided a response rate of 80% before ASCT. Alternatively, Mitoxantrone or Idarubicine were added to IFM-VP with response rate ranging from 60% to 80%. More recently intensive regimen with IFM-VP, Arac-c, Mitoxantrone were used in several programs before ASCT. The first pilot study with VIM3 Arac provided in 75 patients (51 primary failures and 36 relapses on therapy) an impressive response rate of 72% with 32 CR. In the RP 93 study a modified VIM2-Arac was used, 69 patients, including 33 relapses on therapy, were treated with high dose Cyclophosphamide and Etoposide and randomized between immediate ICE intensification versus two additional courses of VIM2-Arac followed by ICE and ASCT. 64% achieved response before ASCT. The 2 yr EFS of 35% vs 15% was in favor of the long arm. In order to reduce the hematotoxicity of VIM2-arac, reinfusion of PBPC stimulated by SCF + GCSF were used in 39 patients before ASCT. An improvement of toxicity was observed but not on the efficacy.

In Hodgkin's lymphoma, a variation of MINE with IFM-Etoposide, Methyl gag and Vinorelbine was used in 100 HL patients with a response rate of 75%. This regimen was integrated prospectively as the main salvage treatment in 157 failures and relapses HL in the H89 study for advanced stages. Responding patients were intensified by BEAM. The 5 yr-survival was 71% for the 101 patients given ASCT and 38% for the 48 patients treated without. ASCT and chemosensitive disease before ASCT were independent prognostic factors.

From these experiences, it is clear that NHL and HL remain sensitive to chemotherapy after relapses. However, the duration response will depend not only on the quality of salvage regimen but on several factors: time to relapse, and/off therapy, prior treatment, stage. Results should be interpreted with these parameters. In NHL large prospective studies with new combination chemotherapy with rituximab are necessary to establish some standard for salvage chemotherapy.

Risk-Adapted therapy for patients with relapsed or primary refractory Hodgkin's Disease
Craig Moskowitz, Andrew Zelenetz, Joachim Yaholom

Multiple studies have determined that patients with relapsed Hodgkin's disease (HD) treated with high dose therapy (HDT) and ASCT have an event free survival (EFS) of 30-45%. Critical issues such as salvage or cytoreductive chemotherapy prior to HDT, the transplant conditioning regimen and prognostic factors at the time of relapse, must have an impact on survival.

Our protocol, using high-dose chemoradiotherapy was an intent to treat program for relapsed and refractory HD. (Moskowitz et al. Blood, 97: 616, 2001). All patients were cytoreduced with 2 biweekly cycles of ICE (Ifosfamide [5gm/m^2 as 24 hr infusion], Carboplatin [AUC = 5] and Etoposide [100mg/m^2 x 3 days]) with G-CSF support. PBPCs were collected following the second cycle of ICE. Responding patients proceeded to ASCT which included involved-field radiotherapy (IFRT) (18-36Gy; b.i.d.) followed either by CBV or cyclophosphamide, etoposide and intensive hyperfractionated TLI (18 Gy). The response rate to ICE was 88%. Successful mobilization of CD34+ cells following ICE and G-CSF occurred in >90% of patients; with a median number of CD34+ cells/kg collected of 7.03 x 10^6. This is superior to either the DHAP (ESHAP) or dexa-BEAM (mini-BEAM) regimens where the median number of CD34+ cells/kg collected was 3.6 and 1.6 respectively. The EFS as analyzed by intent to treat is 58%; and 70% for the transplanted patients.

Response to salvage chemotherapy (e.g. chemosensitive disease) has been used as the major selection criteria to proceed to ASCT but other prognostic factors may also predict for long term EFS in patients with relapsed and refractory HD. Functional imaging with gallium or PET scanning may have important implications for survival for patients with chemosensitive disease and this information will presented at this Lugano meeting.

There are several reports describing prognostic factors identifiable prior to the transplant that predict for a poor outcome with this approach. We and others have determined that the presence of B symptoms, extranodal disease and remission duration < 1 year predicted for a poor EFS. In our previous study patients with 0-1 adverse factors had an EFS of 82% while those with 2 factors had an EFS of 38%, and patients with all 3 factors had an EFS of 15%. The use of prognostic modeling has enabled us to evaluate a risk-adapted approach and determine if further intensification of therapy can overcome adverse prognostic features.

Treatment of Relapsed Aggressive Non-Hodgkin's Lymphomas
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Patients with relapsed or refractory aggressive non-Hodgkin's lymphoma (NHL) have a poor prognosis with standard salvage chemotherapy alone. High-dose chemotherapy and autologous stem cell transplantation will offer relapsed patients an improved survival. However some patients due to other co-morbid illness will not be eligible for transplantation. In addition to be eligible for transplantation, patients must have chemotherapy sensitive disease and the physiologic ability to undergo transplantation. The results from clinical trials with the most frequently used salvage chemotherapy regimens are:

Regimen	# Pts	CR rate	ORR	EFS	OS
DHAP	90	31%	55%	15% (2-yr)	25% (2-yr)
ESHAP	122	37%	64%	10% (40mo)	31% (3-yr)
MINE	48	21%	48%	10% (3-yr)	20% (3-yr)
ICE	163	N/A	66%	25% (40mo)	33% (40mo)
EPOCH	131	24%	74%	10% (6-yr)	26% (6-yr)

New alternative regimens often include the addition of monoclonal antibodies such as Rituxamab, radioimmunotherapy, the use of novel chemotherapeutic agents, or modifications in the administration of agents which may improve the response rates and the ability of patients to go on to transplantation. A variety of novel regimens will be discussed in the symposium today.

Rituximab and Ifosfamide, Mitoxantrone, Etoposide (RIME) with Neupogen® support for B-Cell Non-Hodgkin's Lymphoma prior to and after, High-Dose Chemotherapy and Autologous Stem Cell Support (HDC-ASCT).
Joyce, R.M. Ottaway, J, Regan, Umiel T. M. Tetreault, J. Levine, J. McDermott, D. Hurley, D. Giallombardo, N. Uhl, L. Avigan, D.

Relapse of disease is the primary obstacle to success of high dose chemotherapy for the treatment of Non-Hodgkin's Lymphoma. Tumor cell contamination of peripheral blood progenitor cells (PBSC) and the persistence of minimal residual disease are proposed as contributing factors.

This report evaluates the safety of rituximab, ifosfamide, mitoxantrone and etoposide (RIME) as induction prior to HDC-ASCT. The ability of RIME to eradicate tumors cells from PBSCs is evaluated.

Patients had B-cell lymphomas, either indolent NHL in first or greater relapse, aggressive lymphoma resistant or relapsed, mantle cell lymphoma at any presentation. Patients with aggressive lymphoma with a high or high-intermediate International Prognostic Index risk for relapse could be treated at first remission. Patients were treated with two cycles of RIME. Responding or stable patients underwent a third cycle and PBSC collection. Patients were then treated with HDC-ASCT. Patients in remission after HDC-ASCT were treated with 4 doses of rituximab 100 days post transplant. Tumor cell contamination was measured at baseline and in the PBSC. Serial immunoglobulin levels were measured. Patients were followed for TTF and OS.

Thirty-two were enrolled. Twenty-nine underwent stem cell collection. The response rate to RIME induction was 93% (30/32). Stem cell mobilization was successful in 93% 27/29 of patients. The response rate to RIME Induction and HDC-ASCT was 95% with a confirmed CR of 68%. Median follow-up is 22.8 months the median TTF and OS have not been reached.

There was a significant decline in stem cell tumor cell contamination. This was measured molecularly, immunocytochemically and with clonogenic assays in parallel. There was a significant decline in IgG without an increase in infections.

Sixty percent of patients had transient neutropenia after the post transplant rituximab. RIME is a safe, effective induction and mobilization regimen prior to HDC-ASCT.

Lessons from the ICE (ifosfamide, carboplatin, etoposide) Regimen for Relapsed and Refractory NHL: Measuring the Impact of Second-Line Therapy and the Elucidation of Prognostic Models

Andrew D. Zelenetz, Tarun Kewalramani, Paul Hamlin, Stephen Nimer, Joachim Yahalom, and Craig H. Moskowitz Lymphoma Disease Management Team, Memorial Sloan-Kettering Cancer Center, New York, NY 10021

We sought to develop a second-line regimen that had high anti-tumor efficacy while having limited non-hematologic toxicity and could effectively mobilize hematopoietic progenitor cells. ICE regimen has been the platform for a series of prospective clinical trials and an integrated analysis is presented. One hundred and sixty-three patients (age range 14-71, median 46) with aggressive NHL have been treated with ICE. Fifty-two percent (n=85) had primary refractory disease. Patients were treated with three cycles of ICE at a median interval of 17 days. One hundred patients underwent stem cell collection with a median collection of 8.4 x 10^6 CD34 positive cells per kilogram. The overall response rate was 65%. The overall survival (OS) for the group was 33% with an event free survival (EFS) of 27%. Patients with a CR to ICE had a superior OS in comparison to patient with a PR (64% v 24%; $p<0.001$) suggesting that improvement in the CR rate could result in a superior outcome. We have tested this hypothesis with the addition of rituximab to the ICE regimen (RICE) in a subgroup of patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL). Thirty-one patients are evaluable for response with an OR rate 81% and CR rate of 55%. These compare to historical OR and CR rates in the subgroup of patients with DLBCL of 73% ($p=0.503$) and 28% ($p=0.006$). In a separate analysis of the ICE database, the benefit of ICE in patients with refractory disease was studied. The EFS was 22% based on intention to treat and 44% among transplanted patients. Though the refractory patients are less likely to respond to second-line therapy if they have chemo-sensitive disease the outcome is similar to patients with relapsed disease. This large dataset has enabled us to analyze prognostic factors that influence the outcome to second-line therapy.
In conclusion, the ICE chemotherapy regimen is an excellent platform for second-line therapy in patients with relapsed and refractory aggressive NHL. Modifications such as the addition of rituximab hold promise to further improve the utility of this chemotherapy regimen.

Ligand Pharmaceuticals & Elan Pharmaceuticals, Thursday, June 13, 2002, Room A, 07:30 p.m.
Peripheral T-cell Lymphomas: Where are we?

Overview of peripheral T-cell lymphomas

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Peripheral T-cell lymphomas (PTCL) represent 7.6% of the cases, excluding anaplastic large-cell lymphoma (2.4%) in the non-Hodgkin's lymphoma classification project, where 1378 cases from eight institutions in four continents were evaluated. This study demonstrated that although PTCL remains difficult to diagnose and subclassify, a reliable diagnosis can generally be achieved if proper immunophenotypic analysis is performed.

All PTCLs are clinically aggressive with less than 30% 5 year overall survival. The only exceptionis anaplastic large-cell lymphoma (T/null) with a 5-year median survival of greater than 70%: this subtype will not be considered in this presentation. Data will be presented showing that the concept of grouping PTCL according to cell size into low-grade and high-grade lymphoma lacks clinical significance. Currently the histological subclassificationof PTCL at least when the "not otherwise specified" category is considered, does not recognise meaningful clinical variants, but the possibility of grading according to the number of transformed blasts should be further evaluated.

Clinical results remain largely unsatisfactory and new insight into the differentiation of T-cells is needed in order to better understandthe functionalstatus and the biology of this category of lymphomas.

Molecular Pathology of Peripheral T-Cell Lymphomas and Prognostic Groups

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In North America and Europe, T-cell lymphomas make up only ~10% of non-Hodgkin's lymphomas. Despite a low frequency, these tumors include a wide spectrum of clinical syndromes and histological appearances with widely varying prognoses. Only the anaplastic large T/null cell lymphomas have characteristic cytogenetic and molecular genetic abnormalities.

The only truly indolent T cell lymphomas are mycosis fungoides and chronic or smoldering adult T-cell leukemia/lymphoma. The latter is one of the manifestations of infection by HTLV-1. Aggressive T-cell lymphomas include lymphoblastic T-cell lymphoma, acute adult T-cell leukemia/lymphoma, anaplastic large T/null cell lymphoma, AILD-like T-cell lymphoma, nasal or angiocentric NK cell lymphoma, hepatosplenic T-cell lymphoma, enteropathy associated T-cell lymphoma, subcutaneous paniculitis like T-cell lymphoma, and a group of peripheral T-cell lymphomas that do not fit into one of the previously mentioned syndromes. The antiplastic large T/null cell lymphomas characteristically displayed the CD-30 antigen and have the t(2:5) translocation. These tumors usually overexpress the ALK protein, which is associated with an improved prognosis. The nasal NK cell lymphoma is frequently associated with EBV infection and has a striking geographic variation in occurrence. Enteropathy associated T-cell lymphoma is seen often in patients with poorly treated gluten enteropathy. Hepatosplenic lymphoma has a characteristic histological pattern of growth and immunologic expression. Peripheral T-cell lymphoma NOS represents those aggressive T-cell lymphomas that are only recognized because of expressing T-cell markers.

Lymphoblastic T/null cell lymphomas are treated in a manner similar to T-cell ALL and have a reasonably high cure rate when the bone marrow and CNS are not involved. Anaplastic large T/null cell lymphoma is one of the most curable of all non-Hodgkin's lymphomas with ~60% of all patients having durable responses to their primary regimen. The remaining T-cell lymphomas have a poor prognosis with an overall cure rate of <20%.

Treatment of Peripheral T-cell Lymphoma

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The term peripheral T-cell lymphoma has been used to describe a heterogeneous and rare group of diseases. As a consequence of the rarity and heterogeneity, most published series contain relatively small numbers of patients with diverse disease entities; no consensus has emerged on their best management. Early studies of aggressive histology lymphomas included several diseases recognized as discrete entities in the WHO Classification including peripheral T-cell lymphomas, unspecified; angioimmunoblastic T-cell lymphoma; angiocentric lymphoma; nasal NK cell lymphoma; intestinal T-cell lymphoma; and anaplastic large cell lymphoma (ALCL). ALCL appears to have a more favorable outcome to combination chemotherapy programs than the more common diffuse large B-cell lymphoma. However, the other T-cell lymphomas have a poorer outcome than diffuse large B-cell lymphoma in most large studies. Aggressive conventional dose combination chemotherapy regimens such as LNH-87 achieve complete response rates of about 55% and overall 5-year survival of 35% in T-cell lymphomas other than ALCL, compared to 65% complete response rate and 53% 5-year survival for diffuse large B-cell lymphomas. The difference is in part related to the higher percentage of patients with T-cell tumors having more poor clinical prognostic factors; however, T-cell phenotype appears to be a poor prognostic factor independent of the International Prognostic Index. Nucleosides are active against T-cell tumors and combination nucleoside-based regimens are just beginning to be evaluated. In the salvage setting, high-dose chemotherapy and autologous stem cell transplantation is comparably effective in T-cell and B-cell tumors. It is not clear whether the various disease entities that develop from peripheral T-cells are best treated similarly. International cooperation is necessary to accumulate sufficient numbers of patients staged and treated homogeneously to make progress in the management of peripheral T-cell lymphomas.

The IL-2/IL-15 Receptor System: A Target for Immunotherapy of Leukemia/Lymphoma

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The IL-2 receptor represents an extraordinarily useful therapeutic target in leukemia and lymphoma. The scientific basis for this choice is that normal resting cells do not express IL-2R_, whereas it is expressed by the abnormal T cells in patients with certain lymphoid malignancies or autoimmune disorders, and in individuals rejecting allografts. We have introduced different forms of IL-2R-directed therapy including unmodified murine antibodies to IL-2R_ (anti-Tac), humanized anti-Tac, as well as this antibody armed with toxins or _ and _-emitting radionuclides (eg, ^{212}Bi, ^{213}Bi, and ^{90}Y). Recently, we have been using a three-step pretargeting radioimmunotherapy technique to treat a SCID/NOD murine model of human adult T-cell leukemia (ATL) with an anti-Tac antibody-streptavidin conjugate (anti-Tac SA), which recognizes CD25, followed by ^{213}Bi-DOTA-biotin. By administering the large antibody and the radionuclide linked to a small molecule biotin separately, we markedly augmented the efficacy of systemic radioimmunotherapy of this leukemia/lymphoma.

Purine Analogues for Peripheral T-Cell Lymphomas
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Pentostatin, Fludarabine and Cladribine are structurally similar analogues of adenosine that interfere with the action of a key enzyme in the purine degradation pathway, adenosine deaminase (ADA), and have clinical activity in a wide range of lymphoid malignancies. The high intracellular levels of ADA in normal and malignant T cells provides a rationale for the use of these agents in mature T cell neoplasms. This is a heterogeneous group of rare disorders which often become chemo-resistant, follow an aggressive clinical course, and have a poor prognosis. All 3 purine analogues have been used to treat patients within this group. Data has accrued from small, single centre studies generally conducted in patients with relapsed or refractory disease. A study of Pentostatin in the treatment of 145 patients with a range of mature T cell malignancies seen at The Royal Marsden Hospital, showed that response correlated with disease subtype, with an overall response rate (RR) of 32 % but highest RR for Sezary syndrome at 62%. Other groups have shown similar high RR (35-71%) for Pentostatin single agent therapy of Cutaneous T cell lymphomas (CTCL). Studies in CTCL using the other purine analogues have shown RR of 13-47% for Cladribine and 19% for Fludarabine. More recent studies have examined the use of purine analogues in combination with other therapies. RR have been improved by addition of Interferon to Pentostatin (41%) and Fludarabine (51%) without increasing toxicity. Combination with chemotherapy has also resulted in higher RR but at the cost of increased myelotoxicity. There is no published data on combinations of purine analogues with monoclonal antibodies in T cell malignancy but the efficacy of such combinations in B cell disorders would suggest that this is a strategy, which merits exploration.

T-Cell Receptor (TCR) Vaccines Against T-Cell Lymphoma
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The V region of a TCR is end-coded by a unique combination of V, (D), and J gene segments. This recombination process gives rise to a TCR with unique determinants (Id) that is expressed on the surface of T lymphocytes. Since most T cell malignancies are derived from the clonal proliferation of T lymphocytes, a tumor's TCR can serve as specific targets for anti-tumor immunotherapy. The use of TCR as an immunogen has been evaluated. However, the immune response induced by a V region peptide therapy may result in the deletion or suppression of normal T cells in addition to self-reactive T cells having the same V region. In an attempt to induce an immune response that is specific for tumorigenic T cells without resulting in the deletion of normal T cells, the use of soluble, heterodimeric TCR as immunogens in vaccines for active tumor immunotherapy has been evaluated.

In the C6VL murine T cell lymphoma animal model system, TCR genes have been isolated and the transmembrane encoding domains of the TCR genes replaced by sequences encoding for phosphatidylinosintol-linked cell surface expression. Following vaccination with the TCR linked to keyhole limpet hemocyanin (KLH), specific anti-TCR humoral responses were induced. Both the carrier protein and an adjuvant such as SAF-1 or QS21 were required for optimal responses. These immunizations did not affect the TCR repertoire, which suggested that the immune response was Id specific. The TCR-vaccinated mice were specifically protected from a lethal number of C6VL tumor cells (Okada, et al: J Immunol 159: 5516-5527, 1997). This methodology of TCR vaccines is now been evaluated for possible clinical trials in patients with cutaneous T-cell lymphomas and peripheral T-cell lymphomas.

Biomodulatory strategies for the treatment of peripheral T-cell lymphomas
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Peripheral T-cell lymphomas have a poorer prognosis after conventional chemotherapy than intermediate grade B-cell lymphoma, with lower response rates and response durations. Novel approaches for refractory or relapsed patients have included the use of monoclonal antibodies such as CAMPATH 1-H, which targets CD52 expressing cells, and the interleukin-2 receptor targeted fusion toxin, denileukin diftitox (ONTAK). Recent studies have demonstrated that the clinical activity of both targeted agents and conventional cytotoxic therapies may be enhanced by the RXR-binding retinoid, bexarotene (Targretin), which has been demonstrated to induce expression of a family of RXR-regulated genes, including the IL2R. Bexarotene has been shown to render T-cell lymphoma cells susceptible to ONTAK. Studies are underway to explore the potential synergistic interaction between bexarotene and CHOP chemotherapy. The histone deacetylase inhibitor, depsipeptide, has demonstrated promising clinical activity as a single agent in patients with refractory PTCL in pilot Phase I clinical trials. We demonstrated that low dose interleukin-2is an active agent in T-cell lymphomas and that upregulation of cytotoxic T-cell and NK cell activity occurs in responding patient. The exploitation of immunotherapy in the form of allogeneic stem cell transplantation in PTCL has been less than satisfactory due to high morbidity and poor tumor control in prior studies. We developed a novel conditioning regimen using extracorporeal photopheresis and continuous infusion pentostatin with attenuated total body irradiation which has enabled engraftment of allogeneic stem cells with minimal morbidity and which has resulted in full graft-vs-lymphoma effect with a low incidence of acute or chronic graft-vs-host disease. Studies of alternative host conditioning using T-cell depleting agents as well as adoptive immunotherapy with donor lymphocytes are underway, providing promising alternatives for refractory patients.